Synthesis of bridged thiazolium salts as models for thiamin

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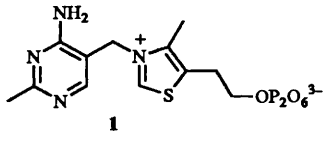
Bridged thiazolium salts **16b** and **c** have been synthesized in a short procedure starting with ω-amino acids. Condensation with carbon disulfide and α-chloro ketone **19** provided thiazole-2(3*H*)-thiones **14b** and **c** and the bridge was then formed by standard macrolactonization procedures. Oxidation of the thiones with hydrogen peroxide then gave the thiazolium salts. The same cyclization procedures failed to yield the shorter bridged compound **15a** but gave the cyclic dimer and trimer. Starting with protected lysine derivatives **31b** and **c**, thiazole-2(3*H*)-thiones **36b** and **c** were obtained. In both cases the cyclization reaction yielded two separable atropisomers depending on which side of the ring the bridge was formed. The catalytic reactions of thiazolium salts **16b** and **c** were compared with unbridged analogues and it was found that, whereas the longer bridged one behaved normally, the shorter bridged salt was unable to catalyse the benzoin condensation. A novel 2-benzoyl-2,3-dihydrothiazole **44** was isolated from this reaction mixture.

Thiamin pyrophosphate **1** is the cofactor used in a number of enzymic reactions in which bonds adjacent to a carbonyl group



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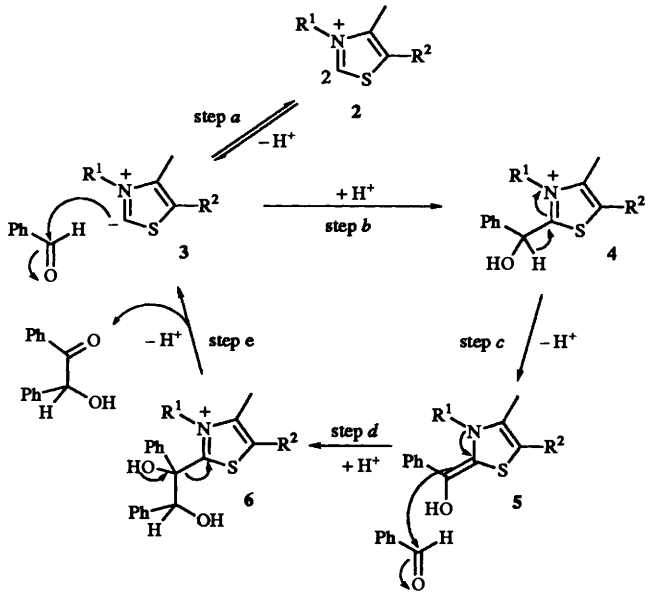
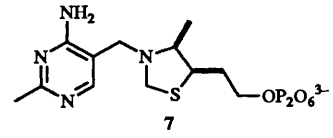
are made or broken.[1] Synthetic thiazolium salts are able to catalyse the same type of reactions non-enzymically. These include decarboxylation of α-keto acids,[2] oxidation of aldehydes by hexacyanoferrate(III),[3] flavins[4] or disulfides,[5] acyloin condensations of aldehydes,[6] and Michael-type addition of aldehydes to enones (Stetter reaction).[7] The same mechanism is thought to be followed for both enzymic and non-enzymic reactions. The mechanism for the benzoin condensation, shown in Scheme 1, was first suggested by Breslow, who showed that



Scheme 1 Mechanism of the benzoin condensation catalysed by a thiazolium salt

the hydrogen on C-2 of thiamin and other thiazolium salts **2** exchanged readily in D_2O at neutral pH, presumably *via* the ylide **3**.[8]

In studies on the pyruvate decarboxylase subunit of the pyruvate dehydrogenase multienzyme complex of *E. coli*, it has been found that the *cis*-isomer of tetrahydrothiamin pyrophosphate **7** is a much more potent inhibitor than the *trans*-isomer **8**.[9] NOE studies revealed that the *cis*-isomer prefers to



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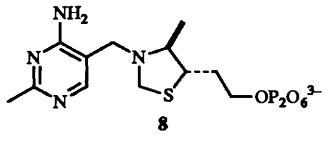

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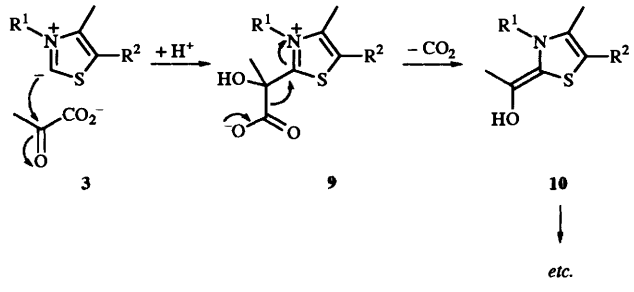
adopt a highly puckered conformation and it was suggested that this isomer binds more tightly to the enzyme because the enzyme exerts strain on the thiazolium ring of thiamin pyrophosphate **1** when it is bound at the active site, tending to bend it out of planarity towards a similar puckered conformation. This, it was argued, would increase the rate of the decarboxylation step at the active site (Scheme 2) as the product **10** would be more easily distorted from planarity than the aromatic thiazolium ring of **9**.[10]



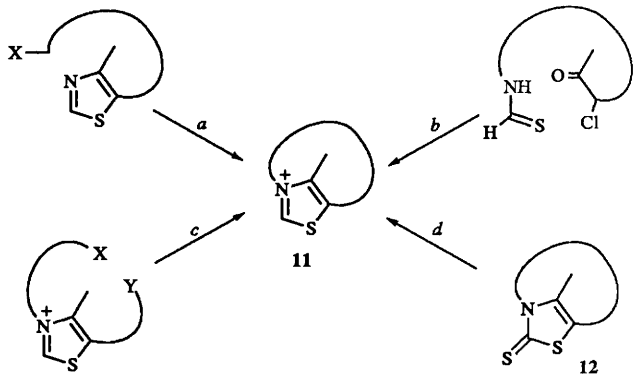
Scheme 2 Mechanism for the decarboxylation of pyruvate

We have, therefore, set out to test this theory by the synthesis of thiazolium salts which are strained by a short bridge between N-3 and C-5. We describe here the synthesis of two such thiazolium salts and our investigations into their catalytic reactions. In a further paper[11] we describe the determination of the con-

formation of the bridged compounds by NMR, X-ray crystallography, and molecular mechanics calculations. Preliminary accounts of part of this work have already been published.[12]

Results and discussion

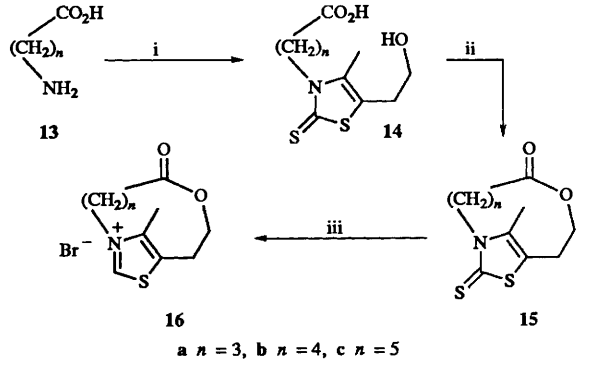
The usual methods for the synthesis of thiazolium salts involve either alkylation of thiazoles[6] (route *a*, Scheme 3) or condens-



Scheme 3 Possible approaches to the synthesis of bridged thiazolium salts

ation of an *N*-substituted thioformamide with an α-chloro ketone (route *b*).[13] If applied to the synthesis of bridged thiazolium salts **11**, these approaches would necessitate the purification of the desired salts from the mixture of compounds expected from such cyclization reactions. After a few unsuccessful attempts, it was realised that these approaches were not viable due to the difficulty in purifying ionic compounds in reasonable quantity by chromatographic methods. For the same reason the synthesis of bridged thiazolium salts by cyclizing a preformed thiazolium salt (route *c*) did not appear promising. Accordingly it was necessary to generate the thiazolium salt from a neutral compound in which the bridge was already in position (route *d*). One suitable way of effecting this is from thiazole-2(3*H*)-thiones, *e.g.* **12**, by oxidation of the thione with hydrogen peroxide under acidic conditions.[14]

It was decided to close the bridge with an ester linkage as a number of well established procedures exist for macrolactonization. Therefore the target was to make bridged thiazolethiones **15** by cyclization of hydroxy acids **14** (Scheme 4). Thiazole-

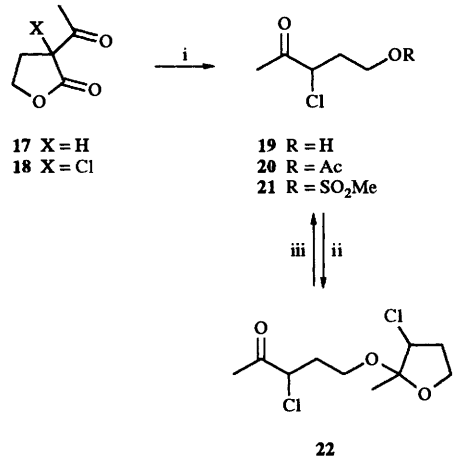


Scheme 4 *Reagents:* i, NaOH, CS_2; **19**; ii, 2-chloro-1-methylpyridinium iodide, Et_3N; iii, H_2O_2, $BaBr_2$

2(3*H*)-thiones can readily be made by the condensation of primary amines with carbon disulfide and α-chloro ketones.[15] Molecular models suggested that the minimum chain length for a bridge between N-3 and C-5 of a thiazole was between 7 and 9 atoms and so syntheses of three bridged compounds, **15a–c**, were attempted.

Synthesis of simple bridged thiazolium salts

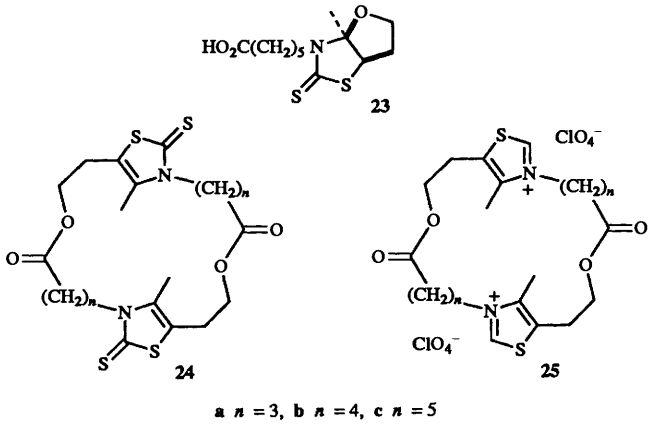
The α-chloro ketone **19** required for the synthesis of thiazolethiones **14** was made by literature procedures[16] from 2-acetylbutyrolactone **17** by chlorination with sulfuryl chloride, followed by hydrolysis and decarboxylation of the product **18** in aqueous acid (Scheme 5). The crude chloro ketone **19** could be



Scheme 5 *Reagents:* i, SO_2Cl_2; H^+, H_2O; ii, distill; iii, H^+, H_2O

used directly in the next reaction or could alternatively be distilled. This distillation, however, caused dimerization with loss of water to give the cyclic acetal **22**, as a mixture of the four possible diastereoisomers. It was best to hydrolyse this acetal in dilute acid before using it for the synthesis of thiazolethiones.

Reaction of the three ω-amino acids **13a–c** with NaOH and CS_2 followed by chloro ketone **19** gave in each case the corresponding thiazole-2(3*H*)-thione **14**. In the synthesis of the highest homologue **14c** an intermediate was isolated which proved to be the bicyclic compound **23**. This intermediate was



converted quantitatively into the desired thiazolethione **14c** by heating with aqueous acid in dioxane and generally the thiazolethiones were synthesized in one pot without isolation of this type of intermediate.

Cyclization of the longest hydroxy acid **14c** was performed using Mukaiyama's procedure[17] (2-chloro-1-methylpyridinium iodide and triethylamine in acetonitrile) and gave an unexpectedly high yield (60%) of the monomeric lactone **15c** along with a small amount (10%) of the dimeric lactone **24c**. The difference between the monomer and the dimer was very apparent in the ^1H NMR spectra as the two hydrogens of every methylene group appear at different chemical shifts for the monomer but are equivalent for the dimer. For the methylene attached to the nitrogen atom of the monomer **15c** the chemical shifts of the two hydrogen atoms differ by 1.36 ppm. The dia-

stereotopic nature of these protons shows that the bridge is too tight to allow rapid rotation of the heterocyclic ring underneath it. If no rotation at all is possible, then the molecules are chiral and the compound might be resolvable into two enantiomers. The larger ring of the dimer, however, does allow rapid rotation of the heterocyclic rings and this makes all the methylene protons equivalent in the NMR spectrum.

The monomeric and dimeric lactones, **15c** and **24c**, could also be distinguished by their UV spectra; the dimer has an absorption maximum at the same wavelength as the unbridged thiazolethiones (321 nm) but the monomer has its absorption maximum at 4 nm higher. No molecular ion was observed for the dimer by electron impact mass spectrometry but the correct molecular weight was obtained using fast atom bombardment (FAB).

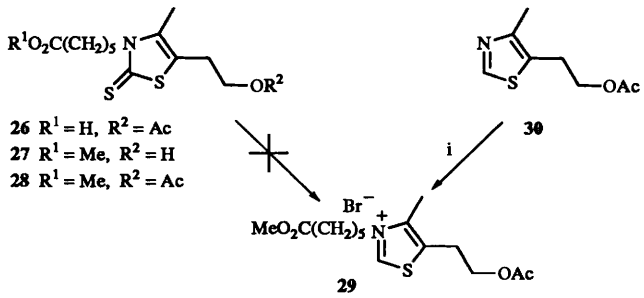
The shorter hydroxy acid **14b**, under the same cyclization conditions as above, yielded only 6% of the corresponding monomeric lactone **15b** along with 11% of the dimeric lactone **24b**. Upon increasing the dilution ten-fold, the yields of monomer and dimer increased to 19 and 24%, respectively, and a trace (2%) of the trimeric lactone was also observed. For the shortest hydroxy acid **14a**, no monomeric lactone **15a** was observed even at very high dilution; only dimer (22%) and trimer (2%) were obtained. For this compound two other cyclization procedures were also tried: Corey and Nicolaou's procedure[18] (triphenylphosphine and dipyridyl disulfide) and Kellogg's procedure[19] (caesium carbonate with the methanesulfonate) both afforded improved yields of the dimer (50 and 58%, respectively) but no monomeric lactone.

The failure of any of the three lactonization procedures to yield even a trace of the monomeric lactone **15a** is an indication that the chain is too short and such a compound would be highly strained. The low yield of **15b** also indicates moderate strain in this compound. More reliable indications of the extent of this strain have come from crystal structures of the thiazolethiones **15a** and **b** and from molecular mechanics calculations. These are described in a separate paper along with NMR studies of the conformation of these molecules in solution.[11]

Conversion of the thiazole-2(3*H*)-thiones into the corresponding thiazolium salts involves oxidation with hydrogen peroxide under acidic conditions. Oxidation of the sulfur atom of the thione occurs, probably to give the sulfinic acid, which then loses SO_2 leaving the thiazolium ylide to be protonated. This process would leave hydrogen sulfate as the counter-ion for the thiazolium salt, which was not desirable for studying the catalytic reactions of these compounds because of its acidity. Accordingly a modified procedure[14] was adopted, involving the inclusion of one equivalent of barium bromide in the reaction mixture in order to precipitate barium sulfate and leave the thiazolium ions **16b** and **c** as their crystalline bromide salts. In addition the dimeric lactone **24a** was also converted into the corresponding bis-thiazolium salt **25a**, isolated as its perchlorate.

In order to compare the catalytic reactions of thiazolium salts **16b** and **c** with an equivalent acyclic model, the synthesis of thiazolium salt **29** was planned (Scheme 6). The corresponding thiazole-2(3*H*)-thione **28** was made both by synthesis of the acetate **26** from chloro ketone **20** followed by methylation with diazomethane and by methylation of acid **14c** followed by acetylation of the resulting alcohol **27**. However, all attempts to convert **28** into the thiazolium salt using acidic hydrogen peroxide failed to give clean product due to hydrolysis of the esters. Eventually the desired salt **29** was made by the alternative route (Scheme 6), alkylation of thiazole **30** with methyl 6-bromohexanoate.

It is interesting that hydrolysis of the lactone was not a problem in the conversion of the bridged thiazolethiones **15b** and **c** to the thiazolium salts **16b** and **c**. Presumably the increase in steric bulk involved in a hydrolysis reaction is disfavoured by the proximity of the ester group to the heterocyclic ring.



Scheme 6 *Reagent:* i, $MeO_2C(CH_2)_5Br$

Investigations into the catalytic reactions of the two monomeric bridged thiazolium salts are described below.

Approaches to chirally bridged thiazolium salts

As noted earlier, the bridged thiazolium salts **16b** and **c** are probably chiral due to the inability of the heterocyclic ring to rotate. This raises the possibility that, if the enantiomers could be separated, these compounds could catalyse the formation of optically active products. Rather than attempt a resolution of the enantiomers, it was decided to make bridged thiazole-2(3*H*)-thiones containing a chiral centre on the bridge. In this way the two stereoisomers produced in the cyclization reaction would be diastereoisomers and should be separable by chromatography.

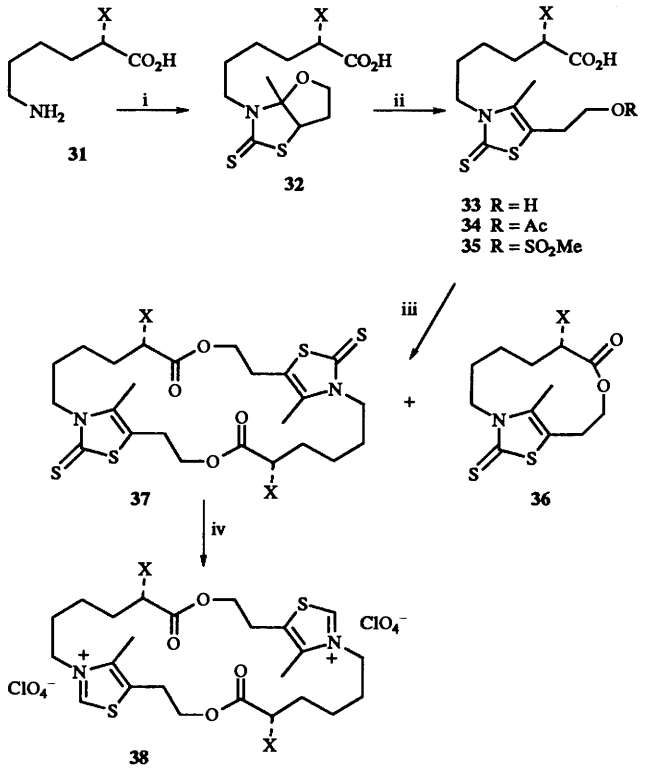
In view of the higher yields for the formation of the longer bridge, it was decided to make a substituted version of thiazolethione **15c**, using a substituted 6-aminohexanoic acid as starting material. It was noted from the X-ray crystal structure of **15c** (see ref. 11) that one of the hydrogen atoms adjacent to the carbonyl group points away from the rest of the molecule and this would therefore be a suitable position for a substitution which did not incur unfavourable steric interactions. The other hydrogen atom adjacent to the carbonyl group lies in a more sterically crowded position and it was expected that the diastereoisomer with a substituent in this position would either have to adopt a different conformation or, if that is not possible, would not be formed at all in significant amounts.

A readily available, optically active 2-substituted 6-aminohexanoic acid is L-lysine **31a**. Protection of the α-amino group was necessary and so two derivatives were made following standard procedures,[20,21] α-*N*-acetyllysine **31b** and the α-dimethylamino derivative **31c** (Scheme 7).

Reaction of the *N*-acetyl derivative **31b** under the usual conditions with NaOH and CS_2 followed by chloro ketone **19** gave not the expected thiazole-2(3*H*)-thione **33b** but the bicyclic precursor **32b**, analogous to the previously isolated compound **23**. To convert **32b** into the desired thiazoline **33b**, it was heated at 60 °C in glacial acetic acid. Heating at reflux in acetic acid was found to give largely the acetate ester **34b** whereas heating in 6 mol dm^{-3} hydrochloric acid hydrolysed the acetamido group also to give **33a**.

Unlike the acetamide, however, the dimethylamino derivative **31c** failed to give any thiazole-2(3*H*)-thione or recognizable precursor under the usual conditions. The desired tertiary amine **33c** was therefore made by methylation of the primary amine **33a** using formaldehyde followed by sodium borohydride.[21]

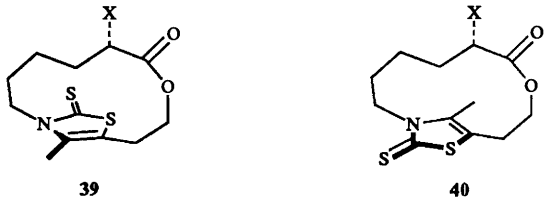
With the hydroxy acids **33b** and **c** both now available, cyclization reactions were attempted. However, it was found that both compounds were highly insoluble in the solvents used in the Mukaiyama and Corey procedures (acetonitrile and toluene respectively) but soluble in dimethylformamide, used in the Kellogg procedure. Mesylation of these compounds using

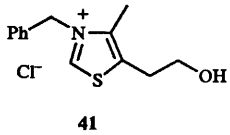


Scheme 7 *Reagents:* i, NaOH, CS_2; **19**; ii, HOAc or 6 mol dm^{-3} HCl; iii, $CsCO_3$, DMF; iv, H_2O_2, $BaBr_2$

dimethylformamide as solvent was not successful and so the methanesulfonates **35b** and **c** had to be made by the alternative route, using the mesyloxychloro ketone **21** in the usual thiazole-2(3*H*)-thione synthesis. In this case, both protected lysine derivatives **31b** and **c** reacted successfully to give **35b** and **c** in good yield.

Attempted cyclization of the methanesulfonate **35b** was performed using caesium carbonate in dimethylformamide at 40 °C for 48 h. The major product isolated from this reaction (30% yield) proved to be the dimeric dilactone **37b** but two other compounds were recovered in very low yields (1.3 and 0.6%), both of which had NMR and mass spectra consistent with being the monomeric lactone **36b**. These are presumably the two expected diastereoisomers **39b** and **40b**. The chemical shifts and





coupling constants of the more major of these lactones are very similar to those for the unsubstituted lactone **15c** and it can be concluded that this is the isomer **39b** where the acetamido group can be accommodated without any major change in conformation. The minor isomer has a very different NMR spectrum and must be due to isomer **40b**, which is forced to adopt quite a different conformation.

Cyclization of the dimethylamino-substituted methanesulfonate **35c**, under the same conditions, again gave three compounds. In this case, however, the yield of the dimeric dilactone **37c** (1.5%) was almost as low as of the monomeric lactones **36c** (1.2 and 0.6%). Again the major monomeric lactone had a similar NMR spectrum to that of **15c** and so can be ascribed structure **39c** and the minor lactone **40c** had a different spectrum corresponding closely to that of **40b**. The spectra and conformations of these bridged compounds are discussed in more detail in ref. 11.

The dimeric lactone **37b**, obtained in relatively high yield, was converted into its corresponding bis-thiazolium salt **38b** but, because of the low yields, there was insufficient material to convert any of the monomeric lactones described in this section into thiazolium salts.

It is possible that if a less polar protecting group was used for the nitrogen atom (such as *tert*-butoxycarbonyl), then the solubility of the hydroxy acid **33** would not have been a problem and the other cyclization methods could have been attempted. Given the results obtained upon cyclization of the methanesulfonate **35b**, however, it is doubtful whether high yields of a monomeric lactone such as **36** could have been obtained by any method and so no further attempts were made to synthesize these compounds. Nevertheless, the synthesis of the bridged compounds **36b** and **c** and the separation of the diastereoisomers has demonstrated that the bridge does introduce chirality and the introduction of an additional chiral centre on the bridge is a viable method for the synthesis of optically pure chiral thiazolium salts.

Catalytic reactions of the bridged thiazolium salts

In order to assess whether the strain of the bridge alters the catalytic reactions of the thiazolium salts **16b** and **c**, they were tested as catalysts for the benzoin condensation (Scheme 1). In this reaction they were compared with two unbridged thiazolium salts, **29** and **41**. This reaction was performed with the catalyst and triethylamine in methanol at 50 °C, under an atmosphere of nitrogen. It was followed both by NMR spectroscopy (in deuteriomethanol) and by GC (with the inclusion of a known amount of 1,2-diphenylethane as a standard). The latter technique was more accurate as it avoids the problem of exchange of the aldehyde proton (and of the corresponding benzoin proton) for deuterium, which occurs by reversal of step *c* in Scheme 1.

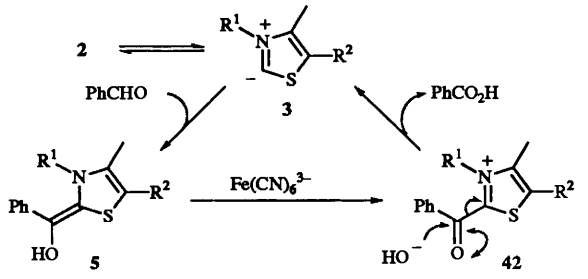
The results from both techniques were qualitatively the same. The standard thiazolium salt **41** reacted fastest, the longer bridged thiazolium salt **16c** reacted at about half the rate, and the unbridged thiazolium salt **29** reacted at a rate intermediate between the two. The shorter bridged thiazolium salt **16b**, however, gave no trace of benzoin by either method. In the NMR experiment the aldehydic proton disappeared slowly (over about 10 h at 50 °C) in the presence of this catalyst, presumably due to exchange. By GC the amount of benzaldehyde decreased by about 20% over 3 h and then remained constant. This decrease corresponds approximately to the amount of catalyst present.

After 5 h the reaction mixtures of the GC experiments were evaporated and redissolved in [$^2H_6$]DMSO to allow determination of the amounts of benzaldehyde and benzoin (relative to the diphenylethane) by NMR spectroscopy. The results for each of the catalysts are given in Table 1.

The inability of the shorter bridged thiazolium salt **16b** to catalyse the benzoin condensation could be because any one of

Table 1 Percentage yields of benzoin produced and benzaldehyde remaining after reaction for 5 h with the various catalysts

	Catalyst			
	41	**29**	**16c**	**16b**
PhCHO (%)	35	38	55	79
Benzoin (%)	63	57	47	0



Scheme 8 Mechanism for the oxidation of benzaldehyde catalysed by a thiazolium salt

the five steps shown in Scheme 1 failed to proceed. It was necessary, therefore, to look at each step in turn, as far as that is possible.

The rate of deprotonation at C-2 of the thiazolium salt (step *a* in Scheme 1) is simply measured by following the exchange of 2-H by NMR spectroscopy. In order to avoid errors due to variation in pH, temperature, buffer concentration, or other factors, the rates of exchange for compounds **16b**, **16c** and **29** were directly compared with that for compound **41** by having them dissolved in phosphate-buffered D_2O in the same NMR tube. It was found in each case that the chemical shift for 2-H of **41** was sufficiently different from that for each of the other three models that the disappearance of the peaks for 2-H in the two compounds could be followed simultaneously. In this way the rates of exchange of 2-H for all the thiazolium salts were compared at pH values between 4.4 and 7.0. The rate of exchange for the bridged compounds **16b** and **c** were indistinguishable from that of **41**, whereas the rate for the unbridged model **29** was marginally slower ($k_{rel.}$ 0.7). Hence the inability of thiazolium salt **16b** to catalyse the benzoin condensation is not due to a failure to generate the corresponding ylide.

The rate of formation of the 'active aldehyde' intermediate **5** can be measured by following its oxidation by compounds such as flavins,[4] quinones or ferricyanide.[3] This reaction is reported to involve rapid oxidation of the intermediate to give the keto thiazolium salt **42** which is hydrolysed to the carboxylic acid with release of the ylide **2** (see Scheme 8). This reaction was performed in a mixture of 10 mmol dm^{-3} phosphate buffer, pH 7.5, and DMSO (60:40) and the disappearance of the hexacyanoferrate(III) absorbance at 420 nm was continuously followed, essentially according to the method of Hilvert and Breslow.[3]

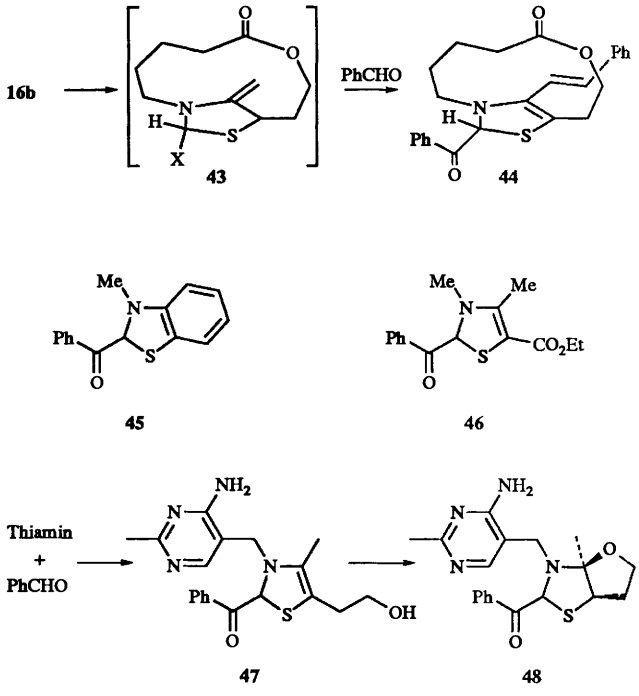
Oxidation rates of four different aromatic aldehydes (*p*-NO_2, *p*-Cl, *m*-Cl, and unsubstituted benzaldehyde) using catalyst **41** and aldehyde concentration of 10 mmol dm^{-3} were measured to assess which was the most suitable aldehyde to use to study the reactions of the bridged catalysts. The rates increased with the electronegativity of the substituent and gave a Hammett ρ value of $+2.5 \pm 0.2$, the better fit being with the σ^- value for the *p*-NO_2 substituent. This value of ρ is consistent with either step *b* or *c* being the rate determining step for this oxidation (see Scheme 2).

The reaction with hexacyanoferrate(III) ions is complicated by the fact that thiazolium salts themselves are slowly oxidized. Therefore a control experiment was always run without added aldehyde and the rate of disappearance of hexacyanoferrate(III) in this control was subtracted from that found in the presence of aldehyde. Initial rates were taken so that loss of the catalyst was not significant. This correction was relatively greater for the aldehydes which reacted more slowly and hence the extra degree of error introduced was greater also. This reaction is therefore best performed with the most reactive aldehyde. For this reason Hilvert and Breslow[3] used *p*-nitrobenzaldehyde but in the present study it was found that this aldehyde reacted with hexacyanoferrate(III), in the absence of thiazolium salts, to give initially a purple byproduct. Therefore the next most reactive aldehyde, *m*-chlorobenzaldehyde, was used instead. This showed no reaction with hexacyanoferrate(III) in the absence of thiazolium salts.

Measurements at different concentrations of reactants confirmed that the reaction is zero-order in hexacyanoferrate(III) and first order in aldehyde up to greater than 10 mmol dm^{-3} (after which the rate begins to level off).

The measured rates of the oxidation of *m*-chlorobenzaldehyde by hexacyanoferrate(III) were approximately equal with all four thiazolium salts as catalysts. The shorter bridged catalyst was, in fact, marginally faster than the other three ($k_{rel.}$ 1.2). It is clear, therefore, that the first three steps (*a*, *b* and *c*) of the benzoin mechanism operate quite normally with the shorter bridged thiazolium salt **16b** as catalyst.

An indication whether it is step *d* or *e* which does not proceed with catalyst **16b**, came from the isolation of a byproduct from an attempted benzoin condensation using this catalyst. An additional UV-absorbing compound was observed by TLC in the reaction mixture of the GC experiment using this thiazolium salt and was purified by preparative TLC. The new compound proved to be a 2-benzoyl-2,3-dihydrothiazole **44** and was obtained from the catalyst in 20% yield.



Scheme 9 Formation of 2-benzoyl-2,3-dihydrothiazole **44** and structures of similar reported compounds

The 2-benzoyl-2,3-dihydrothiazole functionality is clearly derived from one of the intermediates **5** in the benzoin mechanism by enol–ketone tautomerization. This is evidence that the blockage in the mechanism that arises with thiazolium salt **16b** is at the next step, step *d*. 2-Acyl-2,3-dihydrothiazoles such as **44** would not normally be expected to be stable as they would readily revert by enolization to intermediates such as **5** and

thence to **4**. Similar compounds **45–47** have been reported in the reactions of benzaldehyde with benzothiazolium salts[22] (in which the aromaticity of the thiazolium ring is less pronounced), with a 5-ethoxycarbonylthiazolium salt[23] (in which the dihydrothiazole **46** is stabilised by conjugation between the nitrogen lone pair and the ester) and with thiamin[23] (in which the dihydrothiazole is trapped by cyclisation to give the perhydrofurano[2,3-*d*]thiazole **48**). It has been claimed[23] that the 2-benzoyl-2,3-dihydrothiazole **47** accumulates as an intermediate when thiamin is treated with benzaldehyde in basic ethanol (but not more polar solvents) but that it was too unstable to be isolated and reverted to the hydroxybenzylthiamin (as **4**) upon acidification or to thiamin itself upon neutralisation. We are not aware of any simple 2-acyl-2,3-dihydrothiazole with only alkyl substituents having been isolated before. It seems clear that the isolation of **44** as a stable compound in this case is due to the strain of the short bridge. The strain can be partly relieved in compounds where the heterocyclic ring can be significantly puckered and where the nitrogen atom can be distorted towards a tetrahedral as opposed to trigonal geometry. Thus formation of **44** is favoured whereas reversion of an intermediate such as **5** to a thiazolium ion **4** is not. Similarly in order to proceed with the benzoin condensation, attack of **5** on the second aldehyde molecule to form **6** also requires that the nitrogen atom becomes planar and is thus disfavoured by the shorter bridge.

A surprising feature of byproduct **44** is the styryl side-chain formed by condensation between the methyl group of the catalyst **16b** and a benzaldehyde molecule. It is probable that tautomerization of a 2,3-dihydrothiazole generates the enamine **43** (X = COPh or OMe), which then attacks the benzaldehyde. As the yield of this product is only 20%, it is likely that the majority of the catalyst did not react in this manner and as a result was not isolated during the purification procedure (perhaps because of high polarity or lack of UV absorbance).

The anomalous behaviour of the strained, shorter bridged thiazolium salt **16b** is consistent with the suggestion that the effect of this type of strain is to disfavour intermediates in which the nitrogen atom has to be sp^2 hybridized and planar and to favour intermediates in which it can be more easily distorted out of planarity. This effect would be expected to facilitate the loss of CO_2 in the decarboxylation of pyruvate (Scheme 2). In this step the nitrogen atom goes from being obligatorily sp^2 hybridized to a situation where it could be sp^3 hybridized if necessary. Thus the results described here support the theory that strain on the thiazolium ring could be a factor used by pyruvate decarboxylase to enhance its catalytic rate. We hope to be able to test this theory further by additional kinetic experiments on the strained thiazolium salt **16b**.

Experimental

General directions

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Ultra-violet spectra were measured with a Kontron Uvikon 860 spectrophotometer. Infra-red spectra were run on a Perkin-Elmer 297 spectrophotometer. NMR spectra were recorded on Varian EM-360 (60 MHz) and EM-390 (90 MHz) and Bruker WH-250 (250 MHz) and WH-400 (400 MHz) spectrometers. Chemical shifts are quoted on the δ scale relative to tetramethylsilane (TMS) as $\delta = 0$ and J values are given in Hz. For ^{1}H NMR data on all monomeric bridged compounds see ref. 11. Mass spectra were run on AEI MS30 or MS50 machines. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}.

Organic solutions which had been in contact with water were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate before evaporation at about 30 mmHg on a Büchi rotary film evaporator. Analytical thin layer chromatography (TLC) was performed with plates coated with Merck Kieselgel $60F_{254}$ (0.25 mm). Preparative TLC (PLC) was carried out on plates (20 × 20 cm) coated with the same silica gel (1 mm). Column chromatography was performed using Merck Kieselgel 60H.

All solvents were redistilled. Solvents for reactions and reagents were purified before use as follows: acetonitrile—distilled from 1% by weight of phosphorus pentoxide and then from 5% by weight of anhydrous potassium carbonate; benzaldehyde—distilled under argon at reduced pressure and stored under argon; carbon disulfide—treated with bromine, then potassium hydroxide solution, then copper turnings and distilled from calcium chloride in diffuse light; dichloromethane—distilled from phosphorus pentoxide and stored over 4 Å molecular sieves in the dark; diethyl ether (referred to as ether)—distilled from lithium aluminium hydride and stored over sodium wire in the dark; *N*,*N*-dimethylformamide (DMF)—distilled from barium oxide at reduced pressure and stored over 4 Å molecular sieves; methanol—distilled from magnesium methoxide and stored over 4 Å molecular sieves; toluene—distilled and stored over sodium wire.

3-(3-Carboxypropyl)-5-(2-hydroxyethyl)-4-methylthiazole-2(3*H*)-thione 14a

4-Aminobutanoic acid **13a** (1.514 g, 14.7 mmol) and sodium hydroxide (1.216 g, 30.4 mmol) were dissolved in water (10 cm^3). Carbon disulfide (1.22 g, 16.0 mmol) was added and the mixture was stirred for 4 h until the two layers had combined to form a single orange–red liquid phase. The chloro ketone[16] **22** (2.06 g, 15.1 mmol) and carbon disulfide (0.93 g, 12.2 mmol) were added to the solution, which was then heated briefly on the water bath, producing a yellow–orange emulsion. Concentrated hydrochloric acid was added dropwise until the pH was about 5. The organic layer was separated, dissolved in MeOH, dried ($MgSO_4$) and evaporated under reduced pressure to give the hydroxy acid **14a** (1.21 g, 30%) as cubes, mp 120–122 °C (from methanol–chloroform–hexane) (lit.,[24] 115 °C from EtOAc) (Found: C, 46.0; H, 5.65; N, 5.45; S, 25.0%; M$^+$, 261.0487. Calc. for $C_{10}H_{15}NO_3S_2$, C, 45.95; H, 5.80; N, 5.35; S, 24.5%; *M*, 261.0493); λ_{max}(95% EtOH)/nm 322.5; ν_{max}(Nujol)/cm^{-1} 3250 (OH), 3600–2500 (br, CO_2H), 1725 (C=O) and 1605 (C=C); δ_H(250 MHz; CD_3OD) 2.01 (2 H, m, $CH_2CH_2CO_2$), 2.31 (3 H, s, Me), 2.43 (2 H, t, *J* 7, CH_2CO_2), 2.77 (2 H, t, *J* 6, CH_2CH_2OH), 3.67 (2 H, t, *J* 6, CH_2OH) and 4.27 (2 H, m, CH_2N); δ_C(100 MHz; CD_3OD) 13.0 (Me), 23.6, 30.4 and 31.5 (3 × CH_2), 47.7 (CH_2N), 62.1 (CH_2O), 121.4 (C-5), 137.0 (C-4), 175.9 (CO_2H) and 186.7 (C=S); *m*/*z* 261 (80%, M$^+$), 228 (60, M − HS), 175 (25), 158 (25) and 144 (100, $C_6H_{10}NOS^+$).

3-(4-Carboxybutyl)-5-(2-hydroxyethyl)-4-methylthiazole-2(3*H*)-thione 14b

Sodium hydroxide (0.99 g, 24.75 mmol) and 5-aminopentanoic acid **13b** (1.45 g, 12.4 mmol) were dissolved in water (30 cm^3) and carbon disulfide (0.95 g, 12.5 mmol) was added. The mixture was stirred under nitrogen at room temperature, until the carbon disulfide had dissolved to give a single orange phase (about 5 h). Meanwhile, the chloro ketone[16] **22** (1.60 g, 6.27 mmol), 0.2 mol dm^{-3} hydrochloric acid (5 cm^3) and dioxane (5 cm^3) were heated under reflux with stirring for 15 min, then cooled slightly, neutralised to pH 9 with sodium hydrogen carbonate and added to the solution of the dithiocarbamate. The mixture was stirred at 60 °C for 30 min, then cooled to room temperature and acidified dropwise with concentrated hydrochloric acid to pH 1.5, causing an oil to separate out. This mixture was heated at 60 °C for 10 min, at 90 °C for 20 min and then cooled to room temperature and extracted with dichloro-

methane (3 × 30 cm^3). The combined extracts were dried and evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (160 g), eluting with MeOH–$CHCl_3$–AcOH (10:90:2), to give the *hydroxy acid* **14b** (2.56 g, 75%) as plates, mp 81–83 °C (from chloroform–ether) (Found: C, 47.85; H, 6.13; N, 5.08; S, 23.06%; M^+, 275.0668. $C_{11}H_{17}NO_3S_2$ requires C, 47.98; H, 6.22; N, 5.09; S, 23.28%; *M*, 275.0649); R_f (MeOH–$CHCl_3$–AcOH, 10:90:2) 0.30, (10% MeOH in $CHCl_3$) 0.14; λ_{max}(95% EtOH)/nm 321.5; ν_{max}(Nujol)/cm^{-1} 3200–2500 (br, CO_2H), 1700 (C=O) and 1605 (C=C); δ_H(250 MHz; $CDCl_3$) 1.74 (4 H, m, $CH_2CH_2CH_2N$), 2.23 (3 H, s, Me), 2.42 (2 H, t, *J* 6.6, CH_2CO_2), 2.76 (2 H, t, *J* 6.0, CH_2CH_2O), 3.75 (2 H, t, *J* 6.0, CH_2O) and 4.18 (2 H, t, *J* 7.3, CH_2N); δ_C(100 MHz; CD_3OD) 13.0 (Me), 23.1, 28.0, 30.6 and 34.3 (4 × CH_2), 48.3 (CH_2N), 62.3 (CH_2O), 121.5 (C-5), 137.3 (C-4), 177.0 (C=O) and 186.8 (C=S); *m/z* 275 (10%, M^+), 242 (20, M − HS), 141 (80) and 75 (100).

3-(5-Carboxypentyl)-3a-methyl-*trans*-perhydrofurano-[2,3-*d*]-thiazole-2-thione 23

Sodium hydroxide (3.615 g, 90.4 mmol) and 6-aminohexanoic acid **13c** (5.89 g, 44.9 mmol) were dissolved in water (50 cm^3). Carbon disulfide (3.53 g, 46.4 mmol) was added and the mixture was stirred under nitrogen at room temperature until the carbon disulfide had dissolved to give a single orange–red phase (5 h). Meanwhile, the chloro ketone [16] **22** (5.785 g, 22.7 mmol), 0.2 mol dm^{-3} hydrochloric acid (12.5 cm^3) and dioxane (1 cm^3) were heated under reflux for 20 min. The resulting solution was cooled to room temperature, neutralised to pH 9 with sodium hydrogen carbonate and added to the solution of the dithiocarbamate, giving a turbid yellow mixture. The mixture was heated at 80 °C for 15 min to give a clear green solution, acidified to pH 1 with 6 mol dm^{-3} hydrochloric acid, heated again at 90 °C for 30 min, cooled and extracted with ether. The combined organic solutions were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the *thiazolidine-2-thione* **23** (8.76 g, 67%) as plates, mp 80–83 °C (from $CHCl_3$–ether–hexane) (Found: M^+, 289.0785. $C_{12}H_{19}NO_3S_2$ requires *M*, 289.0806); R_f (30% MeOH in $CHCl_3$) 0.75; δ_H(250 MHz; $CDCl_3$) 1.4 (2 H, m, $CH_2CH_2CH_2N$), 1.65 (3 H, s, Me), 1.7 (4 H, m, $CH_2CH_2CH_2CH_2N$), 2.08 (1 H, dddd, *J* 2.0, 5.5, 7.5 and 13.1, $OCH_2CH_AH_B$), 2.36 (2 H, t, *J* 7.4, CH_2CO_2), 2.44 (1 H, m, $OCH_2CH_AH_B$), 3.50 (1 H, ddd, *J* 5.5, 10.8 and 13.5, OCH_AH_B), 3.72 (1 H, m, OCH_AH_B), 3.75 (2 H, m, CH_2N), 4.04 (1 H, ddd, *J* 1.6, 7.5 and 9.1, S-CH) and 7.7 (1 H, br s, OH); *m/z* 289 (20%, M^+), 116 (15), 84 (100) and 83 (25).

3-(5-Carboxypentyl)-5-(2-hydroxyethyl)-4-methylthiazole-2(3*H*)-thione 14c

(*a*) The acid **23** (1.87 g, 6.47 mmol) was dissolved in dioxane (5 cm^3) and 1 mol dm^{-3} hydrochloric acid (90 cm^3) and heated under reflux for 1 h. The solution was extracted with ethyl acetate (2 × 50 cm^3, then 3 × 30 cm^3). The combined extracts were washed with brine (25 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the *hydroxy acid* **14c** (1.87 g, 100%) as needles, mp 119–123 °C (from $CHCl_3$–ether) (Found: C, 49.7; H, 6.6; N, 4.7; S, 21.8. $C_{12}H_{19}NO_3S_2$ requires C, 49.8; H, 6.6; N, 4.8; S, 22.15%); R_f (30% MeOH in $CHCl_3$) 0.62; λ_{max} (EtOH)/nm 321; ν_{max}(Nujol)/cm^{-1} 3400 (OH), 3200–2500 (CO_2H) and 1690 (C=O); δ_H(250 MHz; $CDCl_3$) 1.43 (2 H, m, $CH_2CH_2CH_2N$), 1.67 (2 H, m, $CH_2CH_2CO_2$), 1.74 (2 H, m, CH_2CH_2N), 2.22 (3 H, s, Me), 2.35 (2 H, t, *J* 7.1, CH_2CO_2), 2.75 (2 H, t, *J* 5.9, CH_2CH_2O), 3.74 (2 H, t, *J* 5.9, CH_2O) and 4.14 (2 H, t, *J* 7.5, CH_2N); δ_C(100 MHz; CD_3OD) 13.1 (Me), 25.4, 27.1, 28.1, 30.6 and 34.6 (5 × CH_2), 48.5 (CH_2N), 62.3 (CH_2OH), 121.5 (C-5), 137.2 (C-4), 177.2 (CO_2H) and 186.5 (C=S); *m/z* 289 (M^+), 256 (M − HS) and 144.

(*b*) The procedure for the synthesis of **23** was followed except that after addition of the chloro ketone to the solution of the dithiocarbamate, the mixture was stirred at room temperature for 90 min, then acidified to pH 6 with 2 mol dm^{-3} hydrochloric acid, heated under reflux for 45 min, acidified to pH 1 with conc. hydrochloric acid, heated under reflux for a further hour, then cooled and extracted with chloroform (6 × 20 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the *hydroxy acid* **14c** (65%) as above.

4-Methyl-9-oxo-8-oxa-3,5-nonanothiazole-2(3*H*)-thione 15b

A solution of hydroxy acid **14b** (460 mg, 1.67 mmol) and triethylamine (1.33 g, 13.17 mmol) in acetonitrile (500 cm^3) was added dropwise to a solution of freshly recrystallised 2-chloro-1-methylpyridinium iodide (1.68 g, 6.58 mmol) in acetonitrile (1.4 dm^3) heated at reflux under nitrogen, at a steady rate such that addition was complete in 10 h. After a further hour at reflux the solution was cooled to room temperature and evaporated under reduced pressure. The residue was purified by short column chromatography on silica gel, eluting with 10% EtOAc in CH_2Cl_2, to give the *monomeric lactone* **15b** (83 mg, 19%) as cubes, mp 117.5–119.5 °C (from CH_2Cl_2–ether–hexane) (Found: C, 51.2; H, 5.75; N, 5.45; S, 24.8%; M^+, 257.0550. $C_{11}H_{15}NO_2S_2$ requires C, 51.3; H, 5.87; N, 5.44; S, 24.9%; *M*, 257.0544); R_f (10% EtOAc in CH_2Cl_2) 0.47; λ_{max}(95% EtOH)/nm 325; ν_{max}($CHCl_3$)/cm^{-1} 1725 (C=O); *m/z* 257 (38%, M^+), 224 (20, M − HS) and 157 (100).

Also obtained were: (i) the *dimeric lactone* **24b** (102 mg, 24%) (Found: M^+, 514.1077. $C_{22}H_{30}N_2O_4S_4$ requires M, 514.1088); R_f (10% EtOAc in CH_2Cl_2) 0.42; λ_{max}(95% EtOH)/nm 320.5; ν_{max}($CHCl_3$)/cm^{-1} 1735 (C=O) δ_H(400 MHz; $CDCl_3$) 1.68 (2 × 4 H, m, $CH_2CH_2CH_2N$), 2.18 (2 × 3 H, s, Me), 2.40 (2 × 2 H, t, *J* 5.7, CH_2CO_2), 2.87 (2 × 2 H, t, *J* 5.4, CH_2CH_2O) and 4.23 (2 × 4 H, m, CH_2N and CH_2O); *m/z* 514 (40%, M^+), 481 (3, M − HS), 257 (100), 224 (35) and 157 (40); (ii) the corresponding *trimeric lactone* (8 mg, 2%), R_f (10% EtOAc in CH_2Cl_2) 0.22; λ_{max}(95% EtOH)/nm 321; ν_{max}($CHCl_3$)/cm^{-1} 1730 (C=O); δ_H(400 MHz; $CDCl_3$) 1.71 (3 × 4 H, m, $CH_2CH_2CH_2N$), 2.23 (3 × 3 H, s, Me), 2.39 (3 × 2 H, t, *J* 6.3, CH_2CO_2), 2.86 (3 × 2 H, t, *J* 5.8, CH_2CH_2O) and 4.18 (3 × 4 H, m, CH_2N and CH_2O); *m/z* (FAB + ve ion) 772 (MH^+).

4-Methyl-9-oxo-8-oxa-3,5-nonanothiazole-2(3*H*)-thione 15c

A solution of hydroxy acid **14c** (1.74 g, 6.02 mmol) and triethylamine (4.1 g, 41 mmol) in acetonitrile (400 cm^3) was added dropwise to a solution of freshly recrystallised 2-chloro-1-methylpyridinium iodide (5.15 g, 20 mmol) in acetonitrile (500 cm^3) at reflux under nitrogen, at a steady rate such that addition was completed in 8 h. After a further 30 min at reflux, the solution was evaporated under reduced pressure. The residue was purified by short column chromatography on silica gel, eluting with EtOAc–CH_2Cl_2 (1:1), to give the *monomeric lactone* **15c** (0.988 g, 60%) as cubes, mp 158–161 °C (from EtOAc–CH_2Cl_2–hexane) (Found: C, 52.7; H, 6.25; N, 5.2; S, 23.8. $C_{12}H_{17}NO_2S_2$ requires C, 53.1; H, 6.3; N, 5.2; S, 23.6%); R_f (CH_2Cl_2) 0.13; λ_{max}(95% EtOH)/nm 325; ν_{max}($CHCl_3$)/cm^{-1} 2925 (C–H), 1725 (C=O) and 1615 (C=C), δ_C(100 MHz; $CDCl_3$) 13.9 (Me), 20.2, 23.0, 24.1, 25.9 and 31.4 (5 × CH_2), 46.2 (CH_2N), 60.3 (CH_2O), 118.7 (C-5), 137.1 (C-4), 171.6 (C=O) and 188.0 (C=S); *m/z* 271 (40%, M^+), 238 (60, M − HS) and 157 (100).

Also obtained was the *dimeric lactone* **24c** (164 mg, 10%); R_f (CH_2Cl_2) 0.05; λ_{max}(95% EtOH)/nm 321.5; ν_{max}($CHCl_3$)/cm^{-1} 2930 (C–H) and 1730 (C=O); δ_H(250 MHz; $CDCl_3$) 1.38 (2 × 2 H, m, $CH_2CH_2CH_2N$), 1.67 (2 × 4 H, m, $CH_2CH_2CH_2CH_2N$), 2.22 (2 × 3 H, s, Me), 2.33 (2 × 2 H, t, *J* 7.2,

CH_2CO_2), 2.86 (2 × 2 H, t, *J* 5.4, CH_2CH_2O) and 4.15 (2 × 4 H, m, CH_2N and CH_2O); *m/z* (FAB +ve ion) 543 (MH^+).

4⁴,12⁴-Dimethyl-8,16-dioxo-4²,12²-dithioxo-4²·³,12²·³-tetrahydro-1,9-dioxa-4,12(5,3)-bis(thiazola)hexadecaphane 24a

(*a*) The same procedure was used as in the synthesis of **15c** except using the hydroxy acid **14a** (151 mg, 0.579 mmol) and adding the solution over a period of 10.25 h. Purification by column chromatography on silica gel (60 g), eluting with 10% EtOAc in CH_2Cl_2, gave the *dimeric lactone* **24a** (31 mg, 22%) as prisms, mp 260–263 °C (decomp.) (from chloroform–hexane) (Found: M^+, 486.0758. $C_{20}H_{26}N_2O_4S_4$ requires *M*, 486.0775); R_f (10% EtOAc in CH_2Cl_2) 0.18; λ_{max}(95% EtOH)/nm 322; ν_{max}(Nujol)/ cm^{-1} 1735 (C=O) and 1615 (C=C); δ_H(250 MHz; $CDCl_3$) 1.95 (2 × 2 H, m, $CH_2CH_2CO_2$), 2.15 (2 × 3 H, s, Me), 2.37 (2 × 2 H, t, *J* 7.9, CH_2CO_2), 2.85 (2 × 2 H, t, *J* 5.4, CH_2CH_2O), 4.16 (2 × 2 H, t, *J* 7.5, CH_2N) and 4.22 (2 × 2 H, t, *J* 5.4, CH_2O); *m/z* 486 (40%, M^+), 243 (100), 210 (40) and 157 (35).

Also isolated was the corresponding *trimeric lactone* (3 mg, 2%); R_f (10% EtOAc in CH_2Cl_2) 0.10; δ_H(90 MHz; $CDCl_3$) 2.0 (3 × 2 H, m, $CH_2CH_2CO_2$), 2.25 (3 × 3 H, s, Me), 2.45 (3 × 2 H, t, *J* 7, CH_2CO_2), 2.9 (3 × 2 H, t, *J* 6, CH_2CH_2O) and 4.2 (3 × 4 H, m, CH_2O and CH_2N); *m/z* 569 and 243.

(*b*) Hydroxy acid **14a** (0.130 g, 0.5 mmol), freshly recrystallised 2,2′-dipyridyl disulfide (165 mg, 0.75 mmol) and triphenylphosphine (200 mg, 0.76 mmol) were stirred in dry oxygen-free toluene (20 cm^3) for 5 h, to give a yellow solution. This solution was dripped at a steady rate into stirred dry oxygen-free toluene (100 cm^3) at reflux under a stream of argon, over a period of 8 h. After a further 40 h at reflux, the toluene was distilled off until the volume of solution was 5 cm^3 and the solution was left at room temperature overnight. The precipitated crystals were recrystallized to give the *dimeric lactone* **24a** (61 mg, 50%).

(*c*) The hydroxy acid **14a** (230 mg, 0.88 mmol) was treated with CH_2Cl_2 (40 cm^3) and methyl acetate was added in portions with warming, until the solid had dissolved. The solution was cooled to 0 °C and triethylamine (1.8 g, 18 mmol) was added. Methanesulfonyl chloride (400 mg, 3.5 mmol) was added dropwise to the stirred solution at 0 °C. After 1 h, the mixture was washed with water (2 × 25 cm^3) and saturated brine (25 cm^3) and the combined aqueous layers were then saturated with ammonium sulfate and re-extracted with dichloromethane (3 × 15 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (38 g), eluting with 30% MeOH in $CHCl_3$, to give the methanesulfonate (108 mg, 36%) as an oil; R_f (30% MeOH in $CHCl_3$) 0.52; λ_{max}(95% EtOH)/nm 311.5; ν_{max}(neat)/cm^{-1} 2955, 2845, 3000–2500 (br, CO_2H), 1720 (C=O), 1605 (C=C), 1350 (SO_2) and 1170 (SO_2); δ_H(90 MHz; $CDCl_3$) 2.1 (2 H, m, CH_2CH_2N), 2.3 (3 H, s, 4-Me), 3.0 (2 H, t, *J* 6, CH_2CH_2O), 3.1 (3 H, s, SO_2Me), 2.5 (2 H, t, *J* 7, CH_2CO_2), 4.4–4.2 (4 H, m, CH_2N and CH_2O) and 6.7 (1 H, br, OH).

The methanesulfonate (91 mg, 0.27 mmol) was dissolved in DMF (150 cm^3) and caesium carbonate (145 mg, 0.445 mmol) was added. The mixture was stirred under nitrogen at 40 °C for 19 h and then at room temperature for 48 h. The DMF was removed under reduced pressure and the residue was treated with saturated brine and extracted with dichloromethane. The extract was dried ($MgSO_4$) and evaporated under reduced pressure to give the *dimeric lactone* **24a** (38 mg, 58%).

4-Methyl-9-oxo-8-oxa-3,5-nonanothiazol-3-ium bromide 16b

The thiazolethione **15b** (65 mg, 0.25 mmol) and barium bromide dihydrate (84.4 mg, 0.25 mmol) were dissolved in a mixture of water (5 cm^3) and acetonitrile (5 cm^3). 48% Hydrobromic acid (1 drop) and 30% hydrogen peroxide (10 drops) were added and the solution was left to stand at room temperature and occasionally swirled. The solution turned yellow and slowly began to precipitate barium sulfate. After 3 h the mixture was filtered through Celite and evaporated under reduced pressure to give the *thiazolium salt* **16b** (50 mg, 65%) as prisms, mp 220 °C (decomp.) (from methanol) (Found: C, 43.0; H, 5.15; N, 4.5; S, 10.4; Br, 26.2%; M^+, 226.0895. $C_{11}H_{16}BrNO_2S$ requires C, 43.15; H, 5.25; N, 4.55; S, 10.45; Br, 26.1%; *M* for the cation, 226.0901); λ_{max}(95% EtOH)/nm 261 and 228; ν_{max}(Nujol)/cm^{-1} 1735 (C=O); δ_C(100 MHz; CD_3CN) 13.4 (Me), 18.5, 27.5 and 27.6 (3 × CH_2), 34.7 (CH_2CH_2O), 54.5 (CH_2N), 62.7 (CH_2O), 136.5 (C-5), 145.3 (C-4), 157.3 (C-2) and 172.2 (C=O); *m/z* 226 (3%, cation M^+), 125 (100, $C_6H_8NS^+$) and 55 (40, $C_4H_7^+$).

4-Methyl-9-oxo-8-oxa-3,5-nonanothiazol-3-ium bromide 16c

The thiazolethione **15c** (808 mg, 2.98 mmol) and barium bromide dihydrate (1.045 g, 3.14 mmol) were dissolved in a mixture of water (15 cm^3) and acetonitrile (30 cm^3) with gentle warming. 48% Hydrobromic acid (2 drops) was added and the solution was stirred at 0 °C. 30% Hydrogen peroxide (3.5 cm^3) was added dropwise to the stirred solution, which immediately turned green and slowly began to precipitate barium sulfate. After 3 h the mixture was filtered through Celite and the filtrate was evaporated under reduced pressure to give the *thiazolium salt* **16c** (668 mg, 70%) as hexagonal plates, mp 221–222 °C (from acetone–ethanol–ether) (Found: C, 45.1; H, 5.6; N, 4.5%; M^+, 240.1062. $C_{12}H_{18}BrNO_2S$ requires C, 45.0; H, 5.65; N, 4.4%; *M* for the cation, 240.1058); λ_{max}(95% EtOH)/nm 258 and 220; ν_{max}(Nujol)/cm^{-1} 3070 (C–H), 1725 (C=O) and 1585 (C=N); δ_C(100 MHz; CD_3SOCD_3) 12.8 (Me), 18.6, 22.1, 23.4, 26.9 and 29.9 (5 × CH_2), 53.6 (CH_2N), 62.1 (CH_2O), 136.1 (C-5), 144.2 (C-4), 159.1 (C-2) and 171.8 (C=O); *m/z* 240 (10%, M^+ for cation) and 125 (100, $C_6H_8NS^+$).

4⁴,12⁴-Dimethyl-8,16-dioxo-1,9-dioxa-4,12(5,3)-bis(thiazola)hexadecaphane-4³,12³-diium bis(perchlorate) 25a

The dimeric lactone **24a** (16 mg, 0.033 mmol) was added to glacial acetic acid (2 cm^3) and chloroform was added until the solid dissolved. One drop of 30% aqueous hydrogen peroxide solution was added followed, after 1 h, by 60% aqueous perchloric acid (4 drops) and ether (3 cm^3). After being cooled to 2 °C, the supernatant was decanted to leave the *thiazolium salt* **25a** (15 mg, 73%) as a powder, mp 221–223 °C (from acetonitrile–ether) (Found: C, 38.7; H, 4.55; N, 4.7%. $C_{20}H_{28}N_2O_{12}S_2Cl_2$ requires C, 38.5; H, 4.53; N, 4.5%); λ_{max}(95% EtOH)/nm 260; ν_{max}(Nujol)/cm^{-1} 1720 (C=O); δ_H(250 MHz; CD_3CN) 2.0 (2 H, m, $CH_2CH_2CO_2$), 2.25 (2 H, m, CH_2CO_2), 2.38 (3 H, s, Me), 3.23 (2 H, t, *J* 5.4, CH_2CH_2O), 4.28 (2 H, t, *J* 5.4, CH_2O), 4.38 (2 H, t, *J* 6.9, CH_2N) and 9.42 (1 H, s, 2-H); *m/z* 143 ($C_6H_9NOS^+$), 125 and 112.

5-(2-Acetoxyethyl)-3-(5-carboxypentyl)-4-methylthiazole-2(3*H*)-thione 26

Potassium hydroxide (18.4 g, 0.328 mol) and 6-aminohexanoic acid (36.8 g, 0.281 mol) were dissolved in methanol (100 cm^3) with gentle warming. Carbon disulfide (17.5 cm^3, 0.288 mol) was added dropwise over 25 min to the solution at 0 °C and the solution was stirred for 40 min at 0 °C. A solution of 5-acetoxy-3-chloropentan-2-one [25] **20** (25.00 g, 0.140 mol) in methanol (37 cm^3) was added dropwise over 23 min to the solution at 0 °C. The resulting turbid mixture was stirred for 1 h at 0 °C, then water (200 cm^3) was added in portions over 15 min as the stirred

mixture was allowed to warm to room temperature. The methanol was evaporated under reduced pressure and the remaining solution was acidified to pH 1 with conc. hydrochloric acid. The aqueous layer was decanted off and the resulting yellow oil was dissolved in chloroform (200 cm^3), filtered, dried ($MgSO_4$) and evaporated under reduced pressure to give the *acid* **26** (31.21 g, 67%) as flat prisms, mp 81–82 °C (from chloroform–hexane) (Found: C, 50.5; H, 6.25; N, 4.25; S, 19.7%; M^+, 331.0908. $C_{14}H_{21}NO_4S_2$ requires C, 50.7; H, 6.4; N, 4.25; S, 19.4; *M*, 331.0912); R_f (30% MeOH in $CHCl_3$) 0.66; λ_{max}(95% EtOH)/nm 321.5; ν_{max}($CHCl_3$)/cm^{-1} 3200–2500 (CO_2H), 1730 (ester C=O), 1715 (acid C=O) and 1615 (C=C); δ_H(400 MHz; $CDCl_3$) 1.41 (2 H, m, $CH_2CH_2CH_2N$), 1.66 (2 H, m, $CH_2CH_2CO_2$), 1.71 (2 H, m, CH_2CH_2N), 2.01 (3 H, s, $MeCO_2$), 2.18 (3 H, s, 4-Me), 2.34 (2 H, t, *J* 7.1, CH_2CO_2), 2.81 (2 H, t, *J* 6.3, CH_2CH_2O), 4.09 (2 H, t, *J* 6.3, CH_2O) and 4.11 (2 H, t, *J* 7.2, CH_2N); δ_C(100 MHz; $CDCl_3$) 12.8 (4-Me), 20.8 (CH_3CO), 24.0, 25.9, 26.0, 27.1 and 33.6 (5 × CH_2), 47.5 (CH_2N), 63.1 (CH_2O), 118.3 (C-5), 135.3 (C-4), 170.7 (OCOMe), 179.2 (CO_2H) and 186.0 (C=S); *m*/*z* 331 (30%, M^+), 298 (45, M − HS), 238 (45, M − HS − AcOH), 157 (100) and 144 (30).

5-(2-Acetoxyethyl)-3-(5-methoxycarbonylpentyl)-4-methylthiazole-2(3*H*)-thione 28

(*a*) A solution of diazomethane in ether was added in small portions to a solution of the hydroxy acid **14c** (0.51 g, 1.76 mmol) in methanol (10 cm^3) at 0 °C, until the yellow colour persisted. Evaporation under reduced pressure gave methyl ester **27** (0.57 g) as a yellow oil which was not purified further; δ_H(400 MHz; $CDCl_3$) 1.43 (2 H, m, $CH_2CH_2CH_2N$), 1.68 (2 H, m, $CH_2CH_2CO_2$), 1.74 (2 H, m, CH_2CH_2N), 2.22 (3 H, s, 4-Me), 2.33 (2 H, t, *J* 6, CH_2CO_2), 2.76 (2 H, t, *J* 5, CH_2CH_2O), 3.66 (3 H, s, MeO), 3.76 (2 H, t, *J* 5, CH_2O) and 4.15 (2 H, t, *J* 7, CH_2N); *m*/*z* 303 (M^+), 270 (M − HS) and 144.

Acetic anhydride (0.5 cm^3) was added dropwise to a solution of the methyl ester **27** (0.40 g) in pyridine (5 cm^3) and after 2 h at room temperature further acetic anhydride (5 drops) was added. The solution was briefly warmed to 60 °C and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (15 g), eluting with ether, to give the *diester* **28** (0.31 g, 71%) as a viscous oil (Found: M^+, 345.1075. $C_{15}H_{23}NO_4S_2$ requires *M*, 345.1069); R_f (Et_2O) 0.30; λ_{max}(95% EtOH)/nm 321; ν_{max}(thin film)/cm^{-1} 2930, 2910 and 2840 (C–H), 1730 (C=O) and 1610 (C=C); δ_H(400 MHz; $CDCl_3$) 1.40 (2 H, m, $CH_2CH_2CH_2N$), 1.66 (2 H, m, $CH_2CH_2CO_2$), 1.72 (2 H, m, CH_2CH_2N), 2.02 (3 H, s, $MeCO_2$), 2.22 (3 H, s, 4-Me), 2.31 (2 H, t, *J* 7.4, CH_2CO_2), 2.84 (2 H, t, *J* 6.3, CH_2CH_2O), 3.62 (3 H, s, MeO), 4.10 (2 H, m, CH_2N) and 4.12 (2 H, t, *J* 6.3, CH_2O); *m*/*z* 345 (60%, M^+), 312 (100, M − HS), 252 (30, M − HS − AcOH) and 157 (90).

(*b*) A solution of diazomethane in ether was added in small portions to a solution of the acid **26** (10.07 g, 30.4 mmol) in dry methanol (250 cm^3) until the yellow colour persisted. The solution was evaporated under reduced pressure and a portion (5.52 g) of the residual oil (10.57 g) was purified by column chromatography on silica gel (150 g), eluting with ether, to give the *diester* **28** (4.84 g, 88%) as an oil.

5-(2-Acetoxyethyl)-3-(5-methoxycarbonylpentyl)-4-methylthiazol-3-ium bromide 29

Methyl 6-bromohexanoate[26] (1.00 g, 4.78 mmol) and 5-(2-acetoxyethyl)-4-methylthiazole[27] **30** (0.90 g, 4.86 mmol) were heated at 150 °C for 2 h under nitrogen in a screw-top hard glass tube. After cooling, the mixture was dissolved in dichloromethane (20 cm^3) and extracted with water (2 × 25 cm^3). The combined aqueous layers were washed with ether (10 cm^3) and then evaporated under reduced pressure, removing final traces of water as an azeotrope with benzene, to leave the *thiazolium salt* **29** (1.83 g, 96%) as a gum (Found: M^+, 314.1406. $C_{15}H_{24}NO_4S$ for the cation requires *M*, 314.1426); λ_{max}(95% EtOH)/nm 260 and 220; ν_{max}(thin film)/cm^{-1} 2940 (C–H), 1730 (C=O), 1720 (C=O), 1630 (C=C) and 1585 (C=N); δ_H(250 MHz; CD_3SOCD_3) 1.31 (2 H, m, $CH_2CH_2CH_2N$), 1.55 (2 H, m, $CH_2CH_2CO_2$), 1.82 (2 H, m, CH_2CH_2N), 1.99 (3 H, s, $MeCO_2$), 2.29 (2 H, t, *J* 7.3, CH_2CO_2), 2.53 (3 H, s, 4-Me), 3.32 (2 H, t, *J* 5.8, CH_2CH_2O), 3.54 (3 H, s, MeO), 4.19 (2 H, t, *J* 5.8, CH_2O), 4.58 (2 H, t, *J* 7.4, CH_2N) and 10.45 (1 H, s, 2-H); δ_C(100 MHz; CD_3CN) 11.1 (4-Me), 20.0, 23.8, 24.9, 25.9, 28.6 and 33.0 (5 × CH_2 and $MeCO_2$), 50.8 (MeO), 53.1 (CH_2N), 62.6 (CH_2O), 134.2 (C-5), 143.0 (C-4), 156.6 (C-2), 170.2 (C=O) and 173.4 (C=O); *m*/*z* 314 (5%, cation M^+), 125 (100) and 74 (90).

3-[(5*S*)-5-Acetamido-5-carboxypentyl]-3a-methyl-*cis*-perhydrofurano[2,3-*d*]thiazole-2-thione 32b

Sodium hydroxide (198 mg, 4.95 mmol) and α-*N*-acetyl-L-lysine[20] **31b** (463 mg, 2.46 mmol) were dissolved in water (15 cm^3) and carbon disulfide (200 mg, 2.63 mmol) was added. The mixture was stirred under nitrogen at room temperature for 3 h, giving a single orange phase. Meanwhile the chloro ketone **22** (326 mg, 1.28 mmol), 0.2 mol dm^{-3} hydrochloric acid (6 cm^3) and dioxane (3 drops) were heated at reflux with stirring, for 20 min. This solution was cooled, adjusted to pH 9 with sodium hydrogen carbonate and added to the solution of the dithiocarbamate. The resulting green solution was heated at 80 °C for 20 min, cooled to room temperature and acidified to pH 1 with 6 mol dm^{-3} hydrochloric acid. The mixture was extracted with dichloromethane (4 × 15 cm^3) and the extract was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purifed by column chromatography on silica gel (40 g), eluting with 30% methanol in chloroform, to give the *thiazolidinethione* **32b** (530 mg, 62%) as a powder, mp 105–110 °C (from chloroform–ether); R_f (30% MeOH in $CHCl_3$) 0.4; λ_{max}(95% EtOH)/nm 273.5; ν_{max}(Nujol)/cm^{-1} 3270 (N–H), 3000–2500br (CO_2H), 1710 (C=O acid), 1630 (C=O amide) and 1570 (C=O amide); δ_H(250 MHz; $CDCl_3$) 1.40 (2 H, m, $CH_2CH_2CH_2N$), 1.65 (3 H, s, MeCON) 1.77 (3 H, m, CH_2CH_2N and $NHCHCH_AH_B$), 1.90 (1 H, m, $NHCHCH_AH_B$), 2.04 (3 H, s, MeCO), 2.10 (1 H, m, $OCH_2CH_AH_B$), 2.43 (1 H, dddd, *J* 7.8, 8.9, 10.6 and 13.1, $OCH_2CH_AH_B$), 3.49 (1 H, ddd, *J* 5.7, 10.6 and 14.4, OCH_AH_B), 3.72 (1 H, m, OCH_AH_B), 3.75 (2 H, m, CH_2N), 4.04 (1 H, ddd, *J* 1.4, 7.5 and 8.9, SCH), 4.51 (1 H, dt, *J* 7.5 and 5.2, CHNH), 6.67 (1 H, d, *J* 7.5, NH) and 9.20 (1 H, br, OH); δ_C(100 MHz; $CDCl_3$) 22.6, 22.8, 23.9, 27.2, 31.2 and 35.8 (4 × CH_2 and 2 × Me), 45.6 (C–S), 50.4 (CH_2N), 52.4 (CHNH), 66.8 (CH_2O), 109.5 (CNO), 174.5 and 171.5 (2 × C=O) and 194.1 (C=S); *m*/*z* 346 (20%, M^+), 328 (10, M − H_2O), 313 (15, M − HS), 295 (10, M − H_2O − HS), 269 (10, M − CO_2 − HS), 230 (30), 144 (70), 84 (90) and 60 (100); $[\alpha]_D$ +3 (*c* 0.9, H_2O).

3-[(5*S*)-5-Amino-5-carboxypentyl]-5-(2-hydroxyethyl)-4-methylthiazole-2(3*H*)-thione 33a

The bicyclic compound **32b** (43 mg, 0.12 mmol) was dissolved in 6 mol dm^{-3} hydrochloric acid (10 cm^3) and heated under reflux for 2 h. The solution was evaporated under reduced pressure and the residue purified by short column chromatography on silica gel, eluting with 30% methanol in chloroform, to give the *hydroxyamino acid* **33a** (19 mg, 50%) as prisms, mp above 340 °C (from MeOH–$CHCl_3$–ether); R_f (30% MeOH in $CHCl_3$) 0.11; λ_{max}(water)/nm 317.5; ν_{max}(Nujol)/cm^{-1} 1590 (CO_2^-); δ_H(250 MHz; D_2O) 1.47 (2 H, m, $CH_2CH_2CH_2N$), 1.9–1.7 (4 H, m, CH_2CH_2N and CH_2CHCO_2), 2.30 (3 H, s, Me), 2.85 (2 H, t, *J* 5.9, CH_2CH_2O), 3.57 (1 H, t, *J* 6.1, $CHCO_2$), 3.73 (2 H, t, *J* 5.9, CH_2O) and 4.24 (2 H, t, *J* 7.7, CH_2N); *m*/*z* 304 (5%, M^+), 260

(10, M − CO_2), 227 (100, M − CO_2 − HS), 144 (70) and 84 (50); (FAB +ve ion) 305 (MH^+).

3-[(5*S*)-5-Acetamido-5-carboxypentyl]-5-(2-acetoxyethyl)-4-methylthiazole-2(3*H*)-thione 34b

The bicyclic compound **32b** (880 mg, 2.54 mmol) was dissolved in glacial acetic acid (50 cm^3) and heated under reflux for 45 min. The solution was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (100 g), eluting with 30% methanol in chloroform, to give the *acetamide* **34b** (567 mg, 57%) [along with **33b** (320 mg, 36%)], mp 155–160 °C (from methanol–ether); R_f (30% MeOH in $CHCl_3$) 0.34; λ_{max}(95% EtOH)/nm 321; ν_{max}(Nujol)/cm^{-1} 3270 (N–H), 1740 (C=O ester), 1710 (C=O acid), 1630 (C=O amide) and 1570 (C=O amide); δ_H(250 MHz; CD_3OD) 1.47 (2 H, m, $CH_2CH_2CH_2N$), 1.74 (3 H, m, $CH_AH_BCHCO_2$ and CH_2CH_2N), 1.9 (1 H, m, $CH_AH_BCHCO_2$), 2.00 (3 H, s, MeCONH), 2.04 (3 H, s, $MeCO_2$), 2.28 (3 H, s, 4-Me), 2.92 (2 H, t, *J* 6.2, CH_2CH_2O) and 4.2–4.1 (5 H, m, $CHCO_2$, CH_2N and CH_2O); *m*/*z* 343 (5%, M − CO_2H), 309 (5, M − CO_2H − H_2S) and 79 (100); (FAB +ve ion) 389 (MH^+).

3-[(5*S*)-5-Acetamido-5-carboxypentyl]-5-(2-hydroxyethyl)-4-methylthiazole-2(3*H*)-thione 33b

The bicyclic compound **32b** (320 mg, 0.92 mmol) was dissolved in glacial acetic acid (15 cm^3) and kept at 60 °C for 4.75 h. The acetic acid was then evaporated under reduced pressure as an azeotrope after adding hexane. The oily residue was washed with chloroform (3 × 10 cm^3), evaporated again under reduced pressure and dissolved in methanol. Ether was added quickly to precipitate the *amido acid* **33b** (260 mg, 81%) as a powder, mp 110–120 °C (Found: M^+, 346.1018. $C_{14}H_{22}N_2O_4S_2$ requires *M*, 346.1021); R_f (30% MeOH in $CHCl_3$) 0.15; λ_{max}(95% EtOH)/nm 322; δ_H(250 MHz; CD_3OD) 1.45 (2 H, m, $CH_2CH_2CH_2N$), 1.74 (3 H, m, $CH_AH_BCHCO_2$ and CH_2CH_2N), 1.88 (1 H, m, $CH_AH_BCHCO_2$), 2.00 (3 H, s, MeCO), 2.28 (3 H, s, 4-Me), 2.76 (2 H, t, *J* 6.1, CH_2CH_2O), 3.66 (2 H, t, *J* 6.1, CH_2O), 4.19 (2 H, t, *J* 7.7, CH_2N) and 4.24 (1 H, dd, *J* 5 and 8, $CHCO_2$); *m*/*z* 346 (6%, M^+), 144 (5), 108 (75) and 79 (100).

3-[(5*S*)-5-Carboxy-5-dimethylaminopentyl]-5-(2-hydroxyethyl)-4-methylthiazole-2(3*H*)-thione 33c

Aqueous formaldehyde (37%; 1.5 cm^3) was added to a solution of the amino acid **33a** (385 mg, 1.27 mmol) in methanol (20 cm^3). The solution was heated under reflux under nitrogen for 4 h, with more aqueous formaldehyde (1.5 cm^3) added after 2 h. The solution was then cooled in ice and sodium borohydride (500 mg) was added in small portions over 10 min. The mixture was stirred at 0 °C for a further hour, neutralised with dil. hydrochloric acid and evaporated under reduced pressure. The residue was purified by short flash column chromatography on silica gel, eluting with 30% methanol in chloroform, to give the *dimethylamino acid* **33c** (189 mg, 45%) as a powder, mp 250 °C (decomp.); R_f (30% MeOH in $CHCl_3$) 0.15; λ_{max}(95% EtOH)/nm 322; ν_{max}(Nujol)/cm^{-1} 2700br ($^+$N–H), 1600 (CO_2^-) and 1450 (C=S); δ_H(250 MHz; CD_3OD) 1.55 (2 H, m, $CH_2CH_2CH_2N$), 1.80 (2 H, m, CH_2CH_2N), 1.85 and 1.95 (each 1 H, m, CH_2CHCO_2), 2.28 (3 H, s, 4-Me), 2.76 (2 H, t, *J* 6.0, CH_2CH_2O), 2.86 (6 H, s, NMe_2), 3.47 (1 H, dd, *J* 4.0 and 8.2, $CHCO_2$), 3.66 (2 H, t, *J* 6.0, CH_2O) and 4.21 (2 H, m, CH_2N); δ_C(100 MHz; CD_3OD) 13.0 (4-Me), 23.8, 28.3, 28.6 and 30.6 (4 × CH_2), 42.2 (NMe_2), 48.3 (CH_2N), 62.4 (CH_2O), 71.9 ($CHNMe_2$), 121.8 (C-5), 137.4 (C-4), 173.5 (CO_2H) and 186.9 (C=S); *m*/*z* (FAB +ve ion) 333 (MH^+).

3-Chloro-5-(methylsulfonyloxy)pentan-2-one 21

A mixture of the chloro ketone **22** (10.41 g, 40.8 mmol), water (50 cm^3) and 6 mol dm^{-3} hydrochloric acid (10 drops) was heated under reflux for 1 h. The solution was cooled and extracted with dichloromethane (3 × 40 cm^3). The combined extracts were dried ($MgSO_4$), filtered through cotton wool and then triethylamine (20.0 g) was added. Methanesulfonyl chloride (18.0 g) was added dropwise to the stirred solution at 0 °C and the solution was stirred for a further 1 h. The mixture was filtered through cotton wool, washing with more dichloromethane. The filtrate was washed with water (2 × 100 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ether–hexane (1:1), to give the *methanesulfonate* **21** (11.54 g, 66%; 74% based on unrecovered starting material), as an unstable oil (Found: C, 33.1; H, 5.2. $C_6H_{11}ClO_4S$ requires C, 33.55; H, 5.15%); R_f (ether) 0.44; ν_{max}(thin film)/cm^{-1} 1725 (C=O), 1340 (SO_2) and 1160 (SO_2); δ_H(400 MHz; $CDCl_3$) 2.33 (3 H, s, MeCO), 2.14 and 2.42 (each 1 H, m, CH_2CH_2O), 2.99 (3 H, s, $MeSO_2$), 4.35 (2 H, t, *J* 5.1, CH_2O) and 4.40 (1 H, dd, *J* 4.8 and 8.9, CHCl); δ_C(100 MHz; $CDCl_3$) 26.7 (CH_3CO), 32.4 (CH_2CH_2O), 37.1 ($MeSO_2$), 58.9 (CHCl), 65.9 (CH_2O) and 201.6 (C=O); *m*/*z* 201 and 199 (1 and 3%, M − Me), 121 and 119 (3 and 9, M − $MeSO_3$), 96 (98, $MeSO_3H^+$) and 79 (100, $MeSO_2^+$).

3-[(5*S*)-5-Acetamido-5-carboxypentyl]-5-(2-methylsulfonyloxyethyl)-4-methylthiazole-2(3*H*)-thione 35b

α-*N*-Acetyl-L-lysine **31b** (946 mg, 5.03 mmol) and potassium hydroxide (310 mg, 5.54 mmol) were dissolved in methanol (50 cm^3) and the solution was stirred at 0 °C. Carbon disulfide (0.6 cm^3) was added followed, after 30 min at 0 °C, by methanesulfonate **21** (575 mg, 2.68 mmol) and a further quantity of carbon disulfide (0.6 cm^3). The mixture was stirred at 0 °C for 1 h and at room temperature for 2 h and then acidified to pH 1 with dil. hydrochloric acid. Most of the methanol was evaporated under reduced pressure, the mixture was extracted with chloroform (5 × 20 cm^3) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with 30% methanol in chloroform, to give the methanesulfonate **35b** (700 mg, 62%; 82% based on unrecovered **21**), as an unstable oil, R_f (30% MeOH in $CHCl_3$) 0.17; δ_H(400 MHz; CD_3OD) 1.48 (2 H, m, $CH_2CH_2CH_2N$), 1.74 (3 H, m, CH_2CH_2N and $CH_AH_BCHCO_2$), 1.87 (1 H, m, $CH_AH_BCHCO_2$), 2.01 and 2.02 (together 3 H, 2 × s, MeCON), 2.30 (3 H, s, 4-Me), 3.05 (2 H, t, *J* 5.7, CH_2CH_2O), 3.08 (3 H, s, $MeSO_2$), 4.20 (2 H, t, *J* 7.4, CH_2N), 4.33 (2 H, t, *J* 5.7, CH_2O) and 4.37 (1 H, dd, *J* 4 and 6, $CHCO_2$); δ_C(100 MHz; CD_3OD) 13.4 (4-Me), 22.6 and 22.7, 24.1 and 24.2, 27.6, 28.2 and 32.0 and 32.1 (4 × CH_2 and *Me*CO), 37.6 ($MeSO_2$), 48.6 (CH_2N), 53.8 and 53.9 (CHNH), 70.7 (CH_2O), 119.2 (C-5), 138.9 (C-4), 174.3 and 173.7 (CONH), 175.4 (CO_2H) and 187.0 (C=S); *m*/*z* 328 (30%, M − $MeSO_3H$), 295 (20, M − $MeSO_3H$ − HS), 212 (30), 157 (70), 116 (80), 96 (75, $MeSO_3H$) and 84 (100).

ε-*N*-Benzyloxycarbonyl-α-*N*,*N*-dimethyl-L-lysine

ε-*N*-Benzyloxycarbonyl-L-lysine[20] (5.24 g, 18.7 mmol), methanol (300 cm^3) and 37% aqueous formaldehyde (40 cm^3) were stirred and heated under reflux for 4.5 h and then cooled in ice. Sodium borohydride (5.0 g, 132 mmol) was added in small portions over 30 min. The mixture was stirred at 0 °C for a further 2 h, neutralised to pH 7 with 6 mol dm^{-3} hydrochloric acid and filtered. The filtrate was evaporated under reduced pressure and the residue purified by short flash column chromatography on silica gel, eluting with 30% methanol in chloroform, to give the *dimethylamino acid* (4.87 g, 84%) as a powder, mp 170–175 °C (from EtOH–hexane) (Found: C, 58.9; H, 7.35; N, 8.65%; M^+ 263.1767. $C_{16}H_{24}N_2O_4{\cdot}H_2O$ requires C, 58.9; H, 8.0; N, 8.6%; *M* − CO_2H, 263.1759); R_f (30% MeOH in

$CHCl_3$) 0.2; ν_{max}(Nujol)/cm^{-1} 3250 (N–H), 1705 (NCO_2), 1600 (Ph), 1580 (CO_2^-) and 1540 (N–H); δ_H(250 MHz; D_2O) 1.31 (2 H, m, $CH_2CH_2CH_2N$), 1.50 (2 H, m, CH_2CH_2N), 1.78 and 1.86 (each 1 H, m, CH_2CHCO_2), 2.79 and 2.84 (each 3 H, s, NMe_2), 3.10 (2 H, t, J 6.6, CH_2N), 3.48 (1 H, dd, J 4.4 and 8.0, $CHCO_2$), 5.07 (2 H, s, CH_2O) and 7.4 (5 H, m, Ph); δ_C(100 MHz; D_2O) 23.1, 28.5 and 29.9 (3 × CH_2), 40.1 and 41.2 (NMe_2), 44.3 (CH_2N), 68.8 ($CHNMe_2$), 72.1 (CH_2O), 128.9, 129.6 and 130.0 (3 × phenyl-CH), 137.8 (phenyl-C), 159.5 (CONH) and 174.0 (CO_2H); m/z 263 (30%, M − CO_2H), 174 (20, dimethyllysine), 91 (100, $PhCH_2$), 84 (40) and 58 (70); (FAB +ve ion) 309 (MH^+); $[\alpha]_D$ +17.1 (c 1, H_2O).

α-*N*,*N*-Dimethyl-L-lysine 31c

The foregoing protected dimethyl-L-lysine (850 mg, 2.76 mmol) was dissolved in water (50 cm^3) and acetic acid (6 drops) and 10% palladium-on-charcoal (600 mg) were added. The mixture was hydrogenated for 5 h, then filtered through Celite. The filtrate was evaporated under reduced pressure to give the dimethyl-L-lysine **31c** (447 mg, 93%) as a powder, mp 248–250 °C (from water–ethanol–acetone) (Found: MH^+, 175.1448; M^+, 174.1382. Calc. for $C_8H_{18}N_2O_2$, MH, 175.1447; M, 174.1368); ν_{max}(Nujol)/cm^{-1} 3050 (NH_3^+), 1630 and 1575 (amino acid) and 1540 (NH_3^+); δ_H(250 MHz; D_2O), 1.42 (2 H, m, $CH_2CH_2CH_2N$), 1.71 (2 H, m, CH_2CH_2N), 1.84 and 1.94 (1 H, m, CH_2CHCO_2), 2.86 (6 H, s, NMe_2), 3.00 (2 H, t, J 7.5, CH_2N) and 3.54 (1 H, dd, J 4.3 and 8.7, $CHCO_2$); δ_C(100 MHz; D_2O) 22.8, 27.5 and 28.2 (3 × CH_2), 40.1 (CH_2NH_2), 41 and 44 (br, NMe_2), 71.8 ($CHNMe_2$) and 173.9 (CO_2H); m/z 175 (1.4%, MH^+), 174 (0.2, M^+), 102 (20) and 84 (100).

3-[(5*S*)-5-Carboxy-5-dimethylaminopentyl]-5-(2-methylsulfonyloxyethyl)-4-methylthiazole-2(3*H*)-thione 35c

α-*N*,*N*-Dimethyl-L-lysine **31c** (906 mg, 5.21 mmol) and potassium hydroxide (330 mg, 5.89 mmol) were stirred in methanol (50 cm^3) at 0 °C. Carbon disulfide (0.6 cm^3) was added, followed, after 30 min at 0 °C, by methanesulfonate **21** (598 mg, 2.79 mmol) and a further quantity of carbon disulfide (0.6 cm^3). The mixture was stirred at 0 °C for 1 h and then at room temperature for 1.5 h and then acidified to pH 1 with dil. hydrochloric acid. The methanol was evaporated under reduced pressure, the mixture was extracted with chloroform to remove unchanged **21** and the aqueous layer was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with 30% MeOH in chloroform, to give the *methanesulfonate* **35c** (650 mg, 57%; 72% based on unrecovered **21**) as an unstable oil; R_f (30% MeOH in $CHCl_3$) 0.28; λ_{max}(EtOH)/nm 321; ν_{max}(thin film)/cm^{-1} 1610 (CO_2^-), 1370 (SO_2) and 1160 (SO_2); δ_H(400 MHz; CD_3OD) 1.56 (2 H, m, $CH_2CH_2CH_2N$), 1.78 (2 H, m, CH_2CH_2N), 1.95 (2 H, m, CH_2CHCO_2), 2.31 (3 H, s, 4-Me), 2.84 (6 H, s, NMe_2), 3.05 (2 H, t, J 6.4, CH_2CH_2O), 3.08 (3 H, s, $MeSO_2$), 3.60 (1 H, t, J 6.4, $CHCO_2$), 4.23 (2 H, m, CH_2N) and 4.33 (2 H, t, J 5.9, CH_2O); δ_C(100 MHz; CD_3OD) 13.2 (4-Me), 23.9, 27.4, 28.2 and 28.5 (4 × CH_2), 37.3 ($MeSO_2$), 42.4 (NMe_2), 48.4 (CH_2N), 70.5 (CH_2O), 71.6 ($CHNMe_2$), 118.9 (C-5), 138.7 (C-4), 174.8 (CO_2H) and 187.0 (C=S); m/z 171 (98%), 158 [100, $HO_2CCHNMe_2(CH_2)_3^+$], 138 (80) and 96 (95, $MeSO_3H$).

(10*S*)-10-Acetamido-4-methyl-9-oxo-8-oxa-3,5-nonanothiazole-2(3*H*)-thiones 39b and 40b

The methanesulfonate **35b** (617 mg, 1.46 mmol) was dissolved in dry DMF (500 cm^3) and dry nitrogen was bubbled through the solution for a few minutes. Caesium carbonate (700 mg) was added and the mixture was stirred at 40 °C under a stream of nitrogen for 48 h. The DMF was evaporated under reduced pressure, brine was added to the residue and the mixture was extracted with ethyl acetate. The extract was dried ($MgSO_4$) and evaporated under reduced presure. The residue was purified by column chromatography on silica gel, eluting with 5% methanol in chloroform, followed by PLC on silica gel, eluting four times with dichloromethane–ethyl acetate (1 : 1), to give the following three products.

(i) The *lactone* (major isomer) **39b** (6 mg, 1.3%) as an oil (Found: M^+, 328.0900. $C_{14}H_{20}N_2O_3S_2$ requires M, 328.0915); R_f (10% MeOH in $CHCl_3$) 0.35; λ_{max}($CDCl_3$)/nm 329; m/z 328 (20%, M^+), 295 (25, M − HS), 157 (50), 84 (40) and 60 (100, AcOH).

(ii) The *lactone* (minor isomer) **40b** (3 mg, 0.6%) as an oil (Found: M^+, 328.0890); R_f (10% MeOH in $CHCl_3$) 0.32; λ_{max}($CDCl_3$)/nm 325.5; m/z 328 (10%, M^+), 295 (15, M − HS), 181 (90) and 55 (100, $C_4H_7^+$).

(iii) The *dimeric lactone* **37b** (141 mg, 30%) as needles, mp 283–285 °C (decomp.) (from MeOH–$CHCl_3$–ether). An analytical sample was recrystallised from water–DMF (Found: C, 51.2; H, 6.2; N, 8.3; S, 19.6. $C_{28}H_{40}N_4O_6S_4$ requires C, 51.2; H, 6.15; N, 8.5; S, 19.5%); R_f (10% MeOH in $CHCl_3$) 0.2; δ_H(400 MHz; $CDCl_3$) 1.39 (2 × 2 H, m, $CH_2CH_2CH_2N$), 1.68 (2 × 2 H, m, CH_2CH_2N), 1.77 (2 × 2 H, m, CH_2CHCO_2), 2.03 (2 × 3 H, s, MeCO), 2.24 (2 × 3 H, s, 4-Me), 2.83 (2 × 1 H, ddd, J 3.1, 3.9 and 16.0, $CH_AH_BCH_2O$), 2.97 (2 × 1 H, ddd, J 4.5, 10.1 and 16.0, $CH_AH_BCH_2O$), 3.93 (2 × 1 H, dt, J 14.1 and 6.5, CH_AH_BN), 4.05 (2 × 1 H, dt, J 14.1 and 7.4, CH_AH_BN), 4.24 (2 × 1 H, ddd, J 3.9, 4.5 and 11.0, CH_AH_BO), 4.31 (2 × 1 H, ddd, J 3.1, 10.1 and 11.0, CH_AH_BO), 4.55 (2 × 1 H, td, J 5.0 and 7.5, $CHCO_2$) and 6.24 (2 × 1 H, d, J 7.5, NH); m/z 328, 295, 157 and 149; (FAB +ve ion) 657 (MH^+); $[\alpha]_D$ +43 (c 1.7, DMF).

(10*S*)-10-Dimethylamino-4-methyl-9-oxo-8-oxa-3,5-nonanothiazole-2(3*H*)-thiones 39c and 40c

A solution of methanesulfonate **35c** (880 mg, 2.15 mmol) in dry DMF (500 cm^3) was treated with caesium carbonate (800 mg) for 24 h as in the previous experiment. The same work-up and purification by PLC gave the following three products.

(i) The *lactone* (major isomer) **39c** (8 mg, 1.2%) as an oil (Found: M^+, 314.1135. $C_{14}H_{22}N_2O_2S_2$ requires M, 314.1123); R_f (CH_2Cl_2–EtOAc, 1:1) 0.045; λ_{max}($CDCl_3$)/nm 330; ν_{max} ($CDCl_3$)/cm^{-1} 1725 (C=O); m/z 314 (60%, M^+), 281 (20, M − HS) and 237 (100, M − HS − NMe_2).

(ii) The *lactone* (minor isomer) **40c** (4 mg, 0.6%) as an oil (Found: M^+, 314.1130); R_f (CH_2Cl_2–EtOAc, 1:1) 0.03; λ_{max}($CDCl_3$)/nm 330; m/z 314 (30%, M^+), 281 (20, M − HS) and 237 (100, M − HS − NMe_2).

(iii) The *dimeric lactone* **37c** (10 mg, 1.5%); R_f (CH_2Cl_2–EtOAc 1:1) 0.013; λ_{max}($CDCl_3$)/nm 321.5; δ_H(400 MHz; $CDCl_3$) 1.39 and 1.32 (each 2 × 1 H, m, $CH_2CH_2CH_2N$), 1.64 (2 × 2 H, m, CH_2CH_2N), 1.71 (2 × 2 H, m, CH_2CHCO_2), 2.25 (2 × 3 H, s, 4-Me), 2.39 (2 × 6 H, s, NMe_2), 2.90 (2 × 2 H, t, J 5.7, CH_2CH_2O), 3.27 (2 × 1 H, t, J 7, $CHCO_2$), 4.05 and 3.92 (each 2 × 1 H, dt, J 14.5 and 7.3, CH_2N) and 4.32 and 4.17 (each 2 × 1 H, dt, J 11.3 and 5.7, CH_2O); m/z 628 (M^+), 552 (M − S − NMe_2), 509 (M − S − NMe_2 − $NMeCH_2$), 353 and 314.

(9*S*,19*S*)-9,19-Diacetamido-4^4,14^4-dimethyl-10,20-dioxo-1,11-dioxa-4,14(5,3)bis(thiazola)icosaphane-4^3,14^3-diium 38b

The dimeric thiazolethione **37b** (20 mg, 0.03 mmol) and barium bromide dihydrate (20 mg, 0.06 mmol) were dissolved in DMF (5 cm^3). Water (5 cm^3), 48% hydrobromic acid (1 drop) and 30% aqueous hydrogen peroxide (2 drops) were added. After 2.5 h at room temperature, the mixture was filtered through Celite and

the filtrate was evaporated under reduced pressure to give the *thiazolium salt* **38b** (15 mg, 65%) as a yellow solid; δ_H(250 MHz; D_2O) 1.33 (2 × 2 H, m, $CH_2CH_2CH_2N$), 1.67 (2 × 2 H, m, CH_2CHCO_2), 1.83 (2 × 2 H, m, CH_2CH_2N), 1.99 (2 × 3 H, s, MeCO), 2.48 (2 × 3 H, s, 4-Me), 3.34 (2 × 2 H, t, *J* 5.4, CH_2CH_2O), 4.23 (2 × 1 H, dd, *J* 5.0 and 9.7, $CHCO_2$), 4.47–4.41 (2 × 4 H, m, CH_2O and CH_2N) and 9.78 (2 × 1 H, s, 2-H); *m/z* 171 [3%, $(CH_2)_4CH(NHAc)CO_2^+$], 143 (40, $C_6H_9NOS^+$), 113 [35, $(CH_2)_4CHCO_2^+$] and 112 (100, $C_6H_8O_2^+$).

Measurement of the rate of the benzoin condensation

(a) By NMR. A measured quantity of catalyst (50–180 μmol) was placed in an NMR tube and dissolved in CD_3OD (0.3 cm^3). A measured quantity of Et_3N (100–300 μmol) was then added, the tube was flushed with nitrogen, sealed and equilibrated at 50 °C. A measured quantity of freshly distilled PhCHO (0.18–1.0 mmol) was then added and NMR spectra were recorded after appropriate time intervals.

(b) By GC. Into a 5 cm^3 flask capped with a rubber septum were placed 0.62 mol dm^{-3} benzaldehyde in methanol (1 cm^3), 0.48 mol dm^{-3} triethylamine in methanol (0.25 cm^3) and 0.30 mol dm^{-3} 1,2-diphenylethane in methanol (0.5 cm^3; internal standard for GC analysis). The flask was bubbled with argon saturated with methanol vapour for 10 min and then equilibrated at 50 °C for 10 min. A 0.48 mol dm^{-3} solution of the catalyst in methanol (0.25 cm^3) was then added under argon, giving a molar ratio PhCHO:Et_3N:$(PhCH_2)_2$:catalyst of 5.17:1:1.25:1. The mixture was incubated at 50 °C and, after appropriate time intervals, aliquots (0.1 cm^3) were removed by syringe and added to a mixture of H_2O (1 cm^3) and benzene (0.25 cm^3). After vigorous shaking, the benzene layer was separated and dried over $MgSO_4$. This extract was subjected to GC analysis (column: SGE BP5; 5% phenylmethylsiloxane, 25 m; 100–250 °C). The amount of benzoin was determined by comparison of peak areas with the internal standard. After 5 h, the reaction mixtures were evaporated to dryness at high vacuum for several hours and the residues dissolved in [$^2H_6$]DMSO for NMR analysis. See Table 1 for details.

Measurement of the rate of exchange of 2-H of the thiazolium salts

Buffered D_2O solutions of different pH values were prepared by dissolving Na_2HPO_4 and KH_2PO_4 in D_2O in different proportions, such that the concentration of phosphate was 0.2 mol dm^{-3}. The pH was measured with an appropriate limited-range pH paper. 0.4 mol dm^{-3} Solutions of the thiazolium catalysts, **41**, **16b**, **16c** or **29** (or mixtures of **41** with one of **16b**, **16c** or **29**) in D_2O were also prepared and equal volumes of the catalyst and buffer solutions were added to each other in an NMR tube at time zero. The tube was kept at 22 °C and 90 MHz NMR spectra were recorded at intervals. The peaks corresponding to 2-H were integrated relative to an internal standard (normally the 4-methyl peak).

Measurement of the rate of oxidation of aromatic aldehydes by hexacyanoferrate(III) ions

A septum-capped UV cuvette (1 cm path-length) was flushed out with argon. Into the cuvette were injected a 2.5 mmol dm^{-3} solution of $K_3Fe(CN)_6$ in 10 mmol dm^{-3} pH 7.5 aqueous phosphate buffer (0.96 cm^3) and a 25 mmol dm^{-3} solution of the aldehyde in DMSO (0.96 cm^3). The cuvette was equilibrated at 30 °C and then a 2.5 mmol dm^{-3} solution of the catalyst in DMSO (0.48 cm^3) was added. The absorbance at 420 nm was continuously measured. ε_{420} was measured to be 1040 dm^3 mol^{-1} cm^{-1} for $K_3Fe(CN)_6$.

The following parameters were varied for different experiments: (*i*) concentration of $K_3Fe(CN)_6$; (*ii*) pH; (*iii*) the aldehyde used; (*iv*) the concentration of aldehyde; (*v*) the catalyst used; (*vi*) the concentration of the catalyst.

2-Benzoyl-4-(2-phenylvinyl)-2,3-dihydro-8-oxa-3,5-octanothiazol-9-one 44

The residue from evaporation of the reaction mixture of the GC experiment using **16b** as the catalyst (37 mg, 0.12 mmol) was purified by PLC on silica gel, eluting with hexane–ether (1:1), to give the *lactone* **43** as a bright yellow gum (10 mg, 20%) (Found: M^+, 419.1531. $C_{25}H_{25}NO_3S_2$ requires *M*, 419.1555); R_f (hexane–ether, 1:1) 0.2; $\lambda_{max}(CDCl_3)$/nm 284; $\nu_{max}(CDCl_3)$/cm^{-1} 1720 (lactone C=O), 1680 (ketone C=O) and 1600 (C=C); δ_C(100 MHz; $CDCl_3$, assignments were made using off-resonance decoupling at δ 5.93 in the ^1H spectrum in order to assign C-2 unambiguously) 25.4 and 26.4 (2 × CH_2, t), 27.5 (CH_2, dd), 35.8 (CH_2CH_2O, t), 54.5 (CH_2O, dd), 58.8 (CH_2N, dd), 72.8 (C-2, s), 117.2 (Ph–C=*C*, d), 124.5 (C-5, s), 126.6, 127.6, 128.4, 128.6, 128.7 and 133.1 (6 × phenyl-CH, d), 130.8 (Ph–*C*=C, d), 133.8 (C-4, s), 137.5 and 141.0 (2 × phenyl-C, s), 173.0 (lactone C=O, s) and 187.6 (ketone C=O, s); *m/z* 419 (3%, M^+), 314 (100, M − PhCO) and 105 (55, $PhCO^+$).

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